Physiological Modeling

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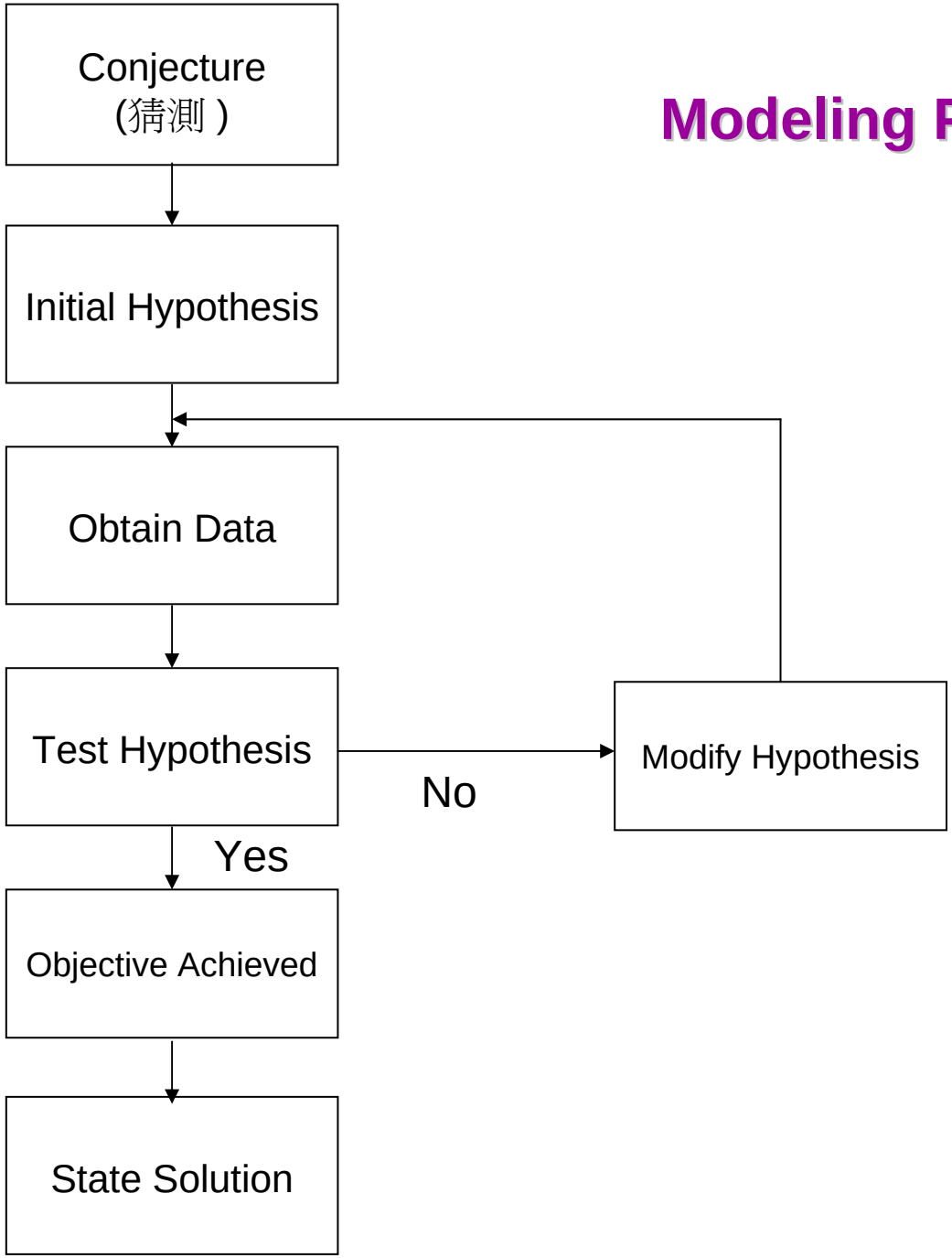
Modeling Process



Types of Physiological Modeling

- Qualitative physiological models
  - Most often used by biologists
  - Describe the actual physiological system without the use of mathematics
- Quantitative physiological models
  - Mathematical representation of the behavior of an actual physiological system

Engineering and Physiological Modeling Process

- **Forward solution**
  - Design and building a system
  - Use a model to predict how the system will behave
- **Inverse solution**
  - Observe the behavior of a system
  - Characterize a system with a model

Exact and Numerical Solutions

$$\ddot{x} + 4\dot{x} + 3x = 9$$

with initial conditions $x(0) = 0$ and $\dot{x}(0) = 1$, the solution is found as

$$x(t) = -4e^{-t} + e^{-3t} + 3$$

A numerical or simulation solution exists for models that have no closed-form solution. Consider the following function:

$$x = \int_{-20}^{20} \frac{1}{33\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{t-7}{33}\right)^2} dt$$

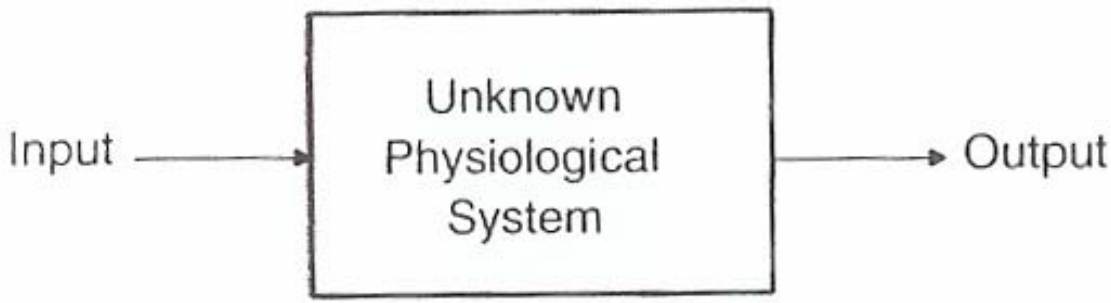
Types of Physiological Modeling

- Deterministic models
  - Exact solution exists
- Stochastic models
  - Involving random variables that are function of time and include probabilistic considerations
  - For a given set of initial conditions, a different solution is given each and every time

Stochastic Models in Biology

- Examples:
  - Drug resistant tumor cells
  - HIV infection
  - Gene mutation

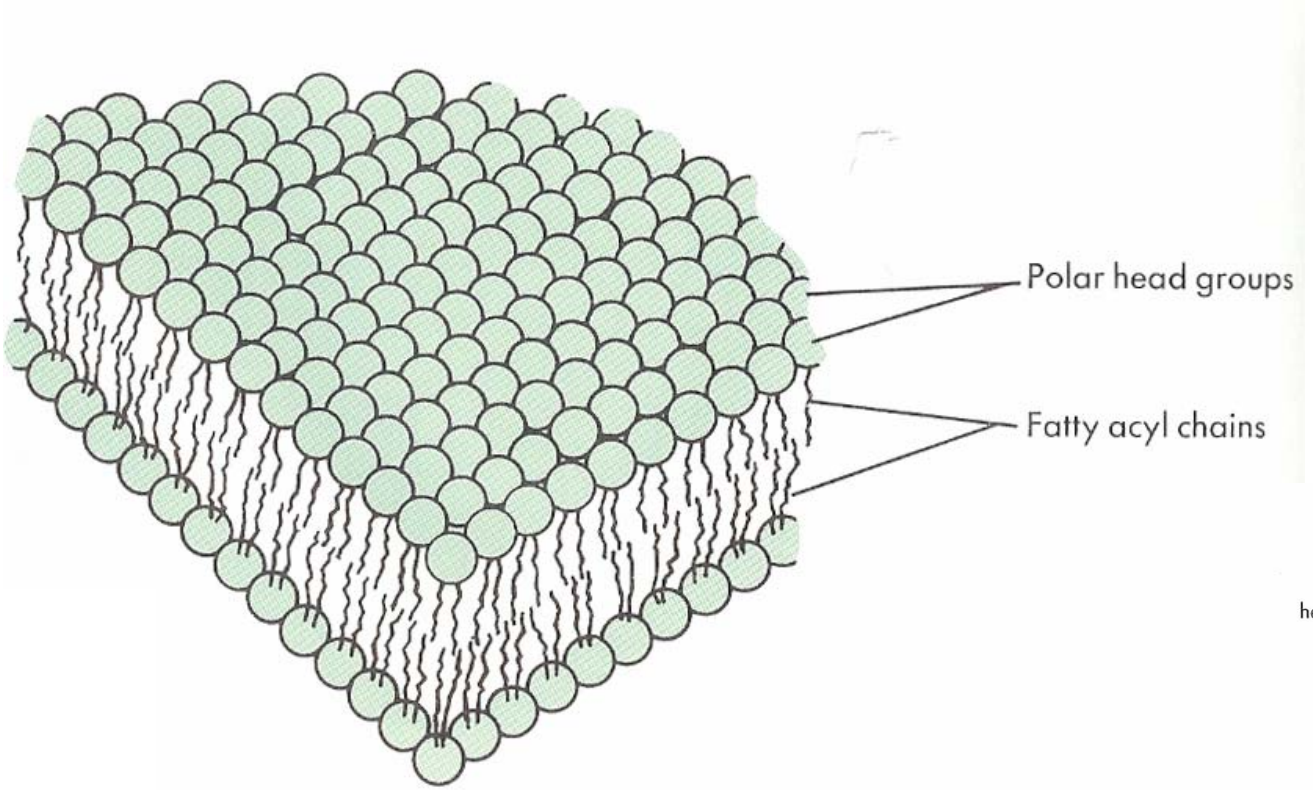
System Identification

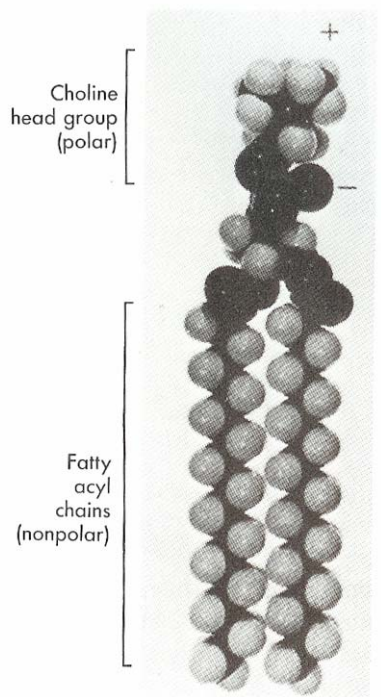


$$H(s) = \frac{V_o(s)}{V_i(s)}$$

Transfer function

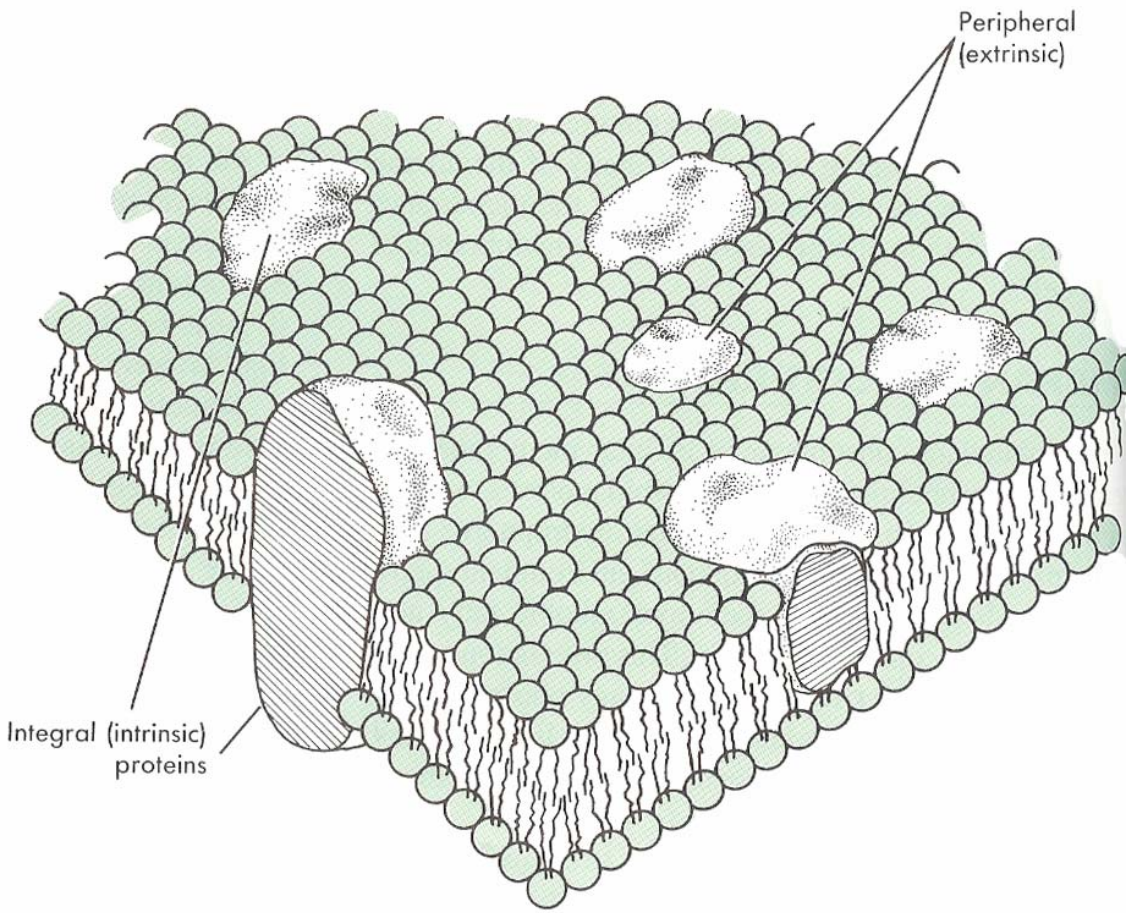
Qualitative physiological models





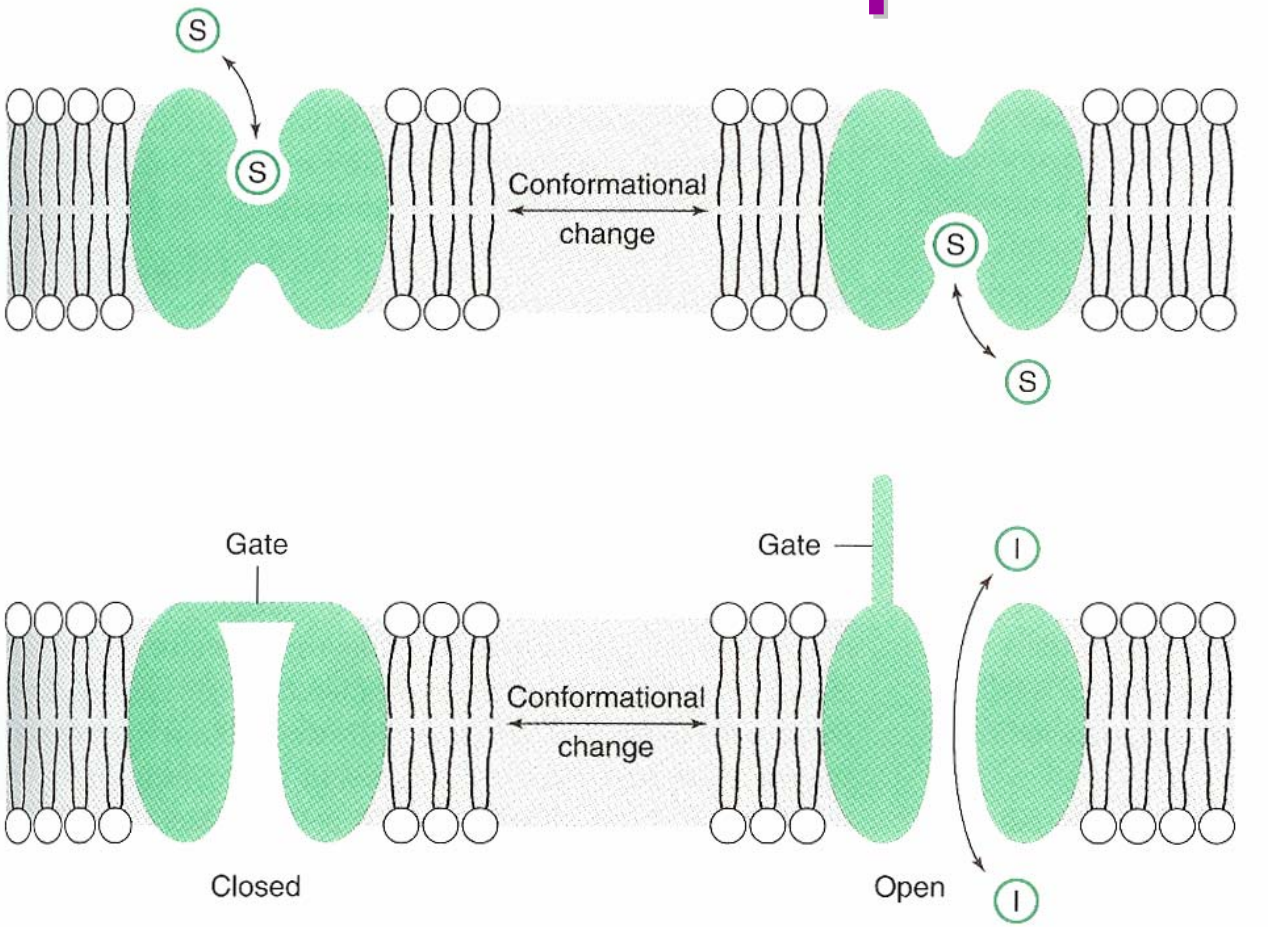
A

Lipid bilayer -- phospholipids

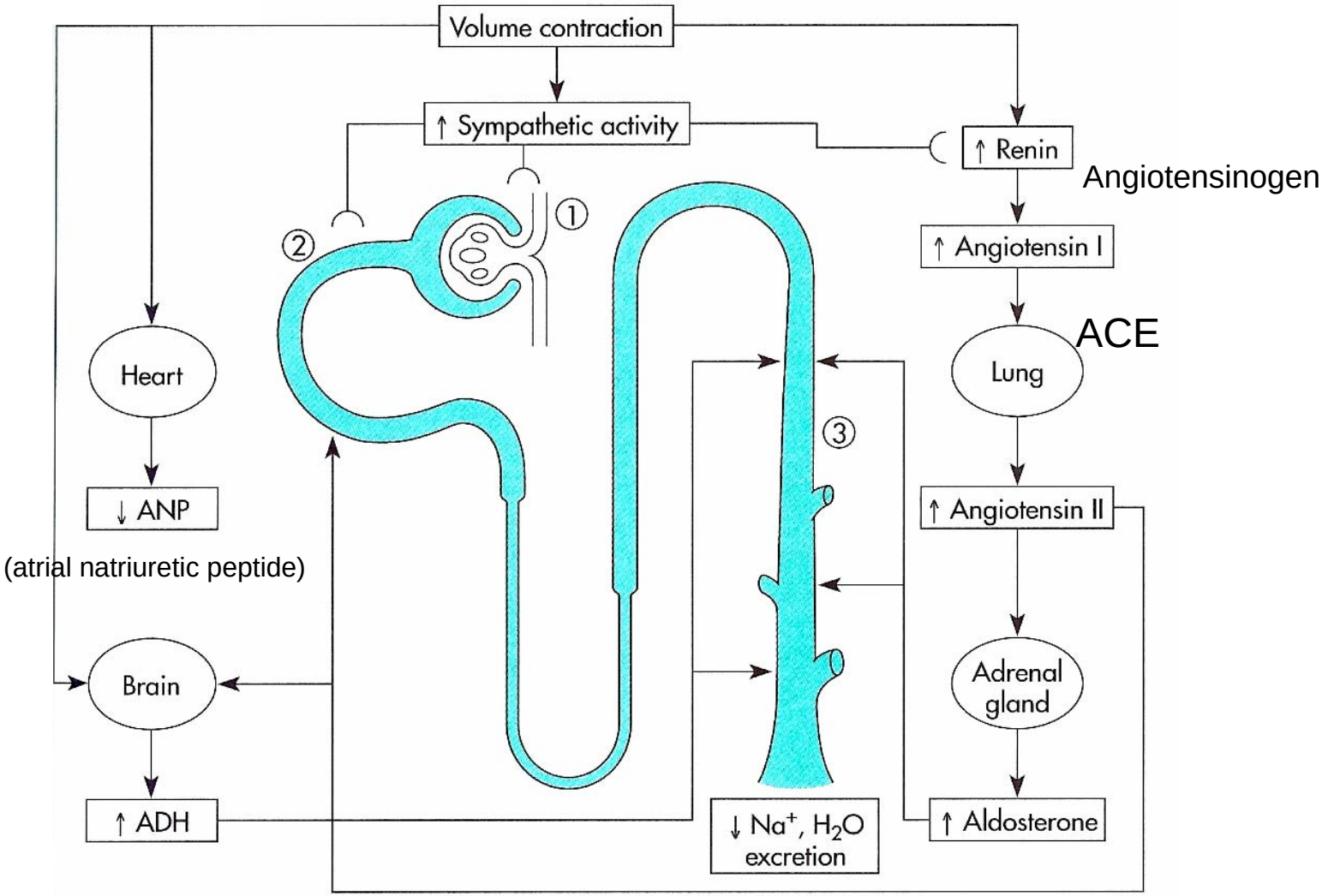


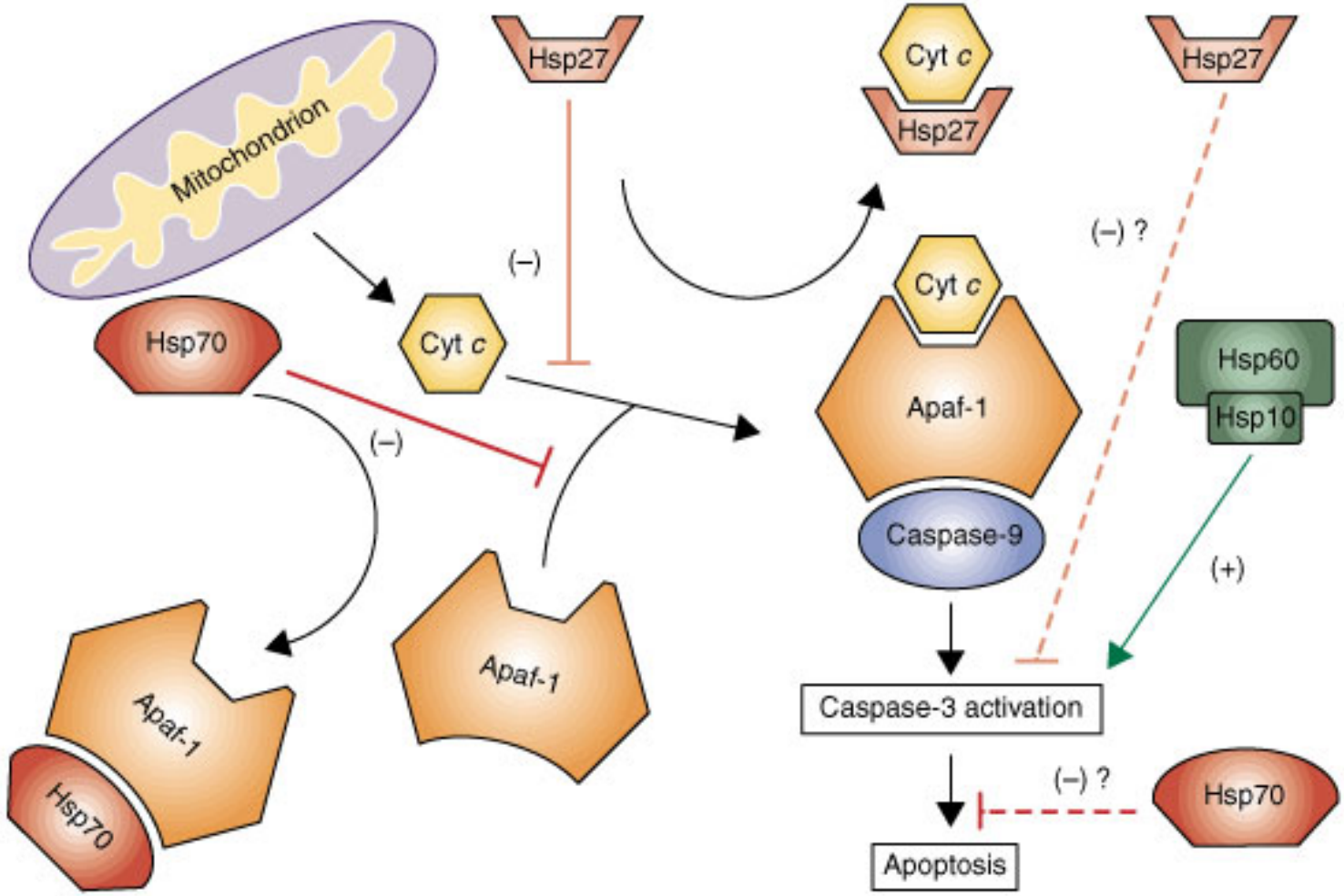
Fluid mosaic model

Membrane Transportation Models



Renin-angiotensin system





Nature Cell Biology, Sep. 2000, ***pp E163 - E165***

Home Work

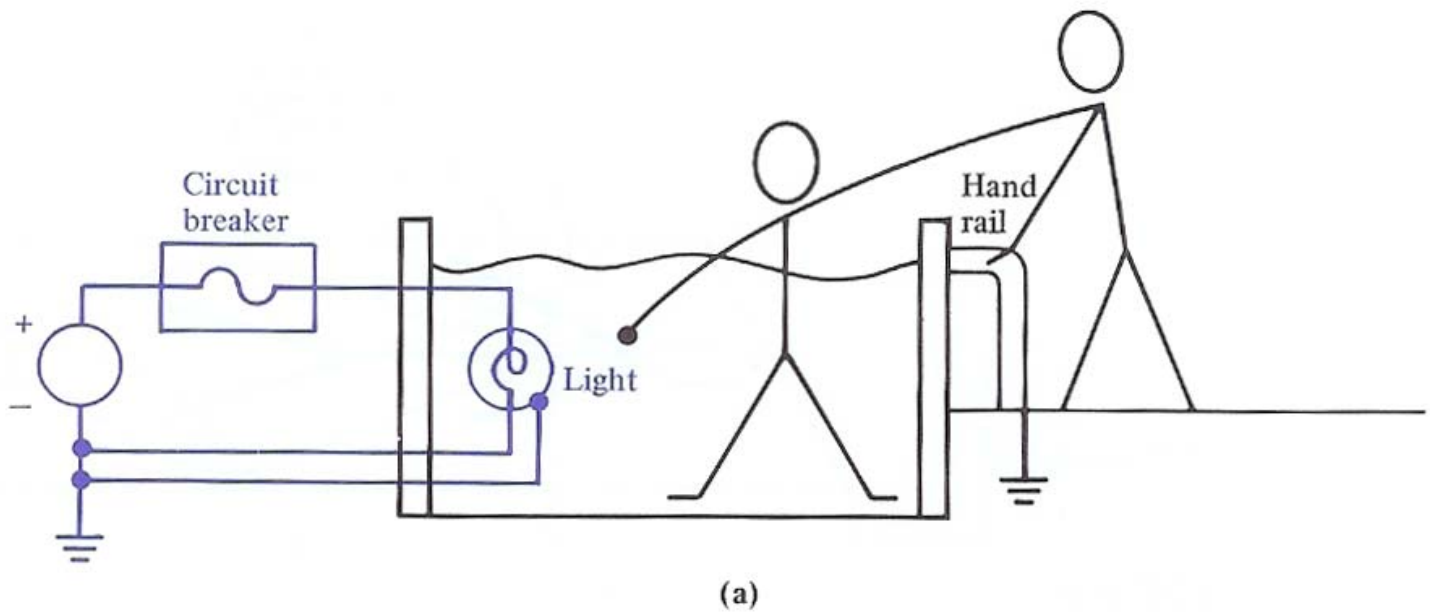
- Briefly explain the apoptosis model in the previous slide (one page, in English).

- What you can learn from this homework:
  - Know how to download a paper from the e-journal database of the medical library?
  - Get experience of reading a short biological paper and understand the key issue in it?
  - Find help from friends who know molecular biology. This/these person(s) may your partner(s) in your future work.
  - Practice English writing.

Quantitative Modeling

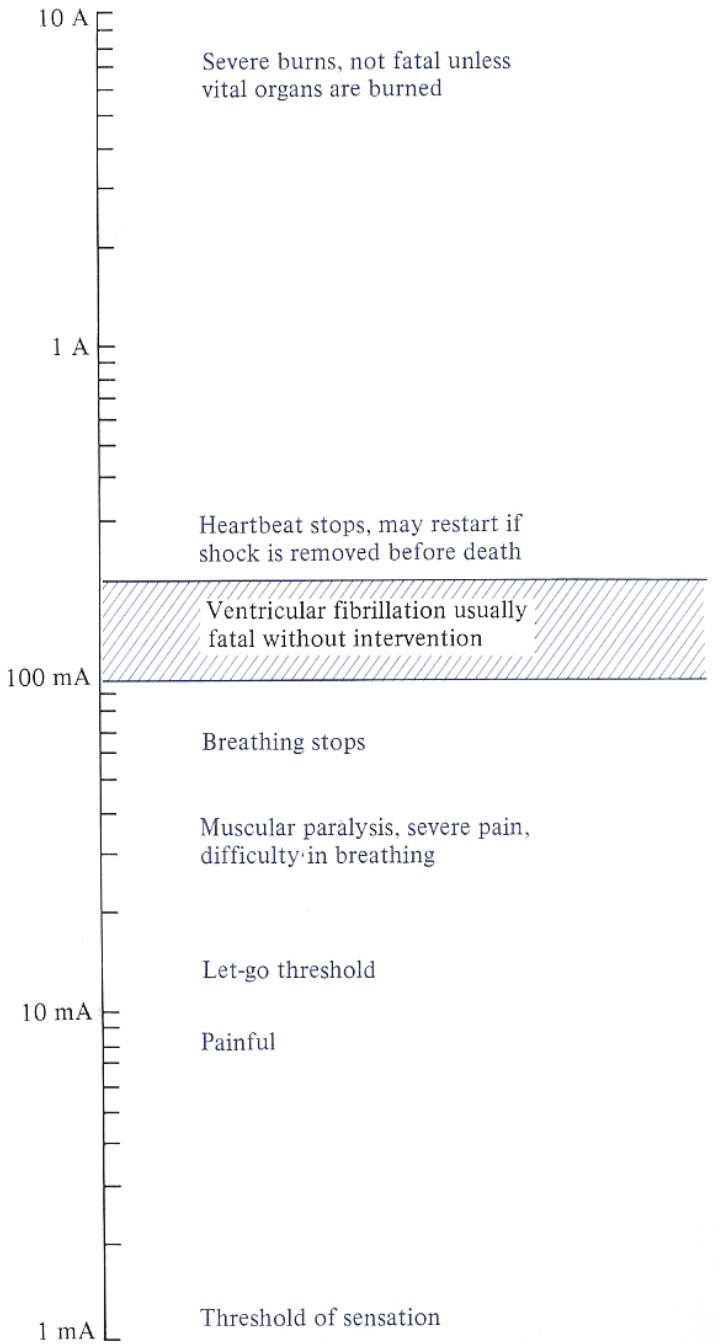
Forward solution

Example 1



(a)

Electrical Safety



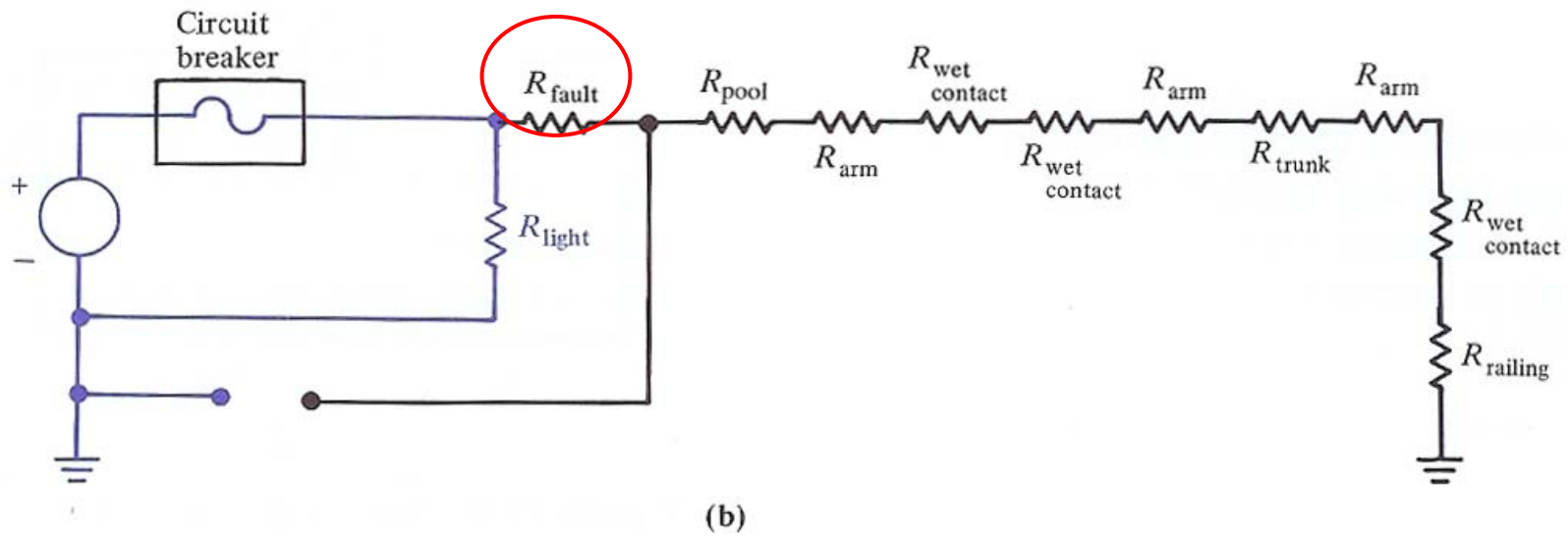
$V = I*R$

$R_{skin\ (dry)} = 15k\Omega$

$R_{skin\ (wet)} = 150\Omega$

$R_{limb\ (arm\ or\ leg)} = 100\Omega$

$R_{trunk} = 200\Omega$



(b)

Figure 21.7 Diagrams used in Example 21.4.

through the two boys would be

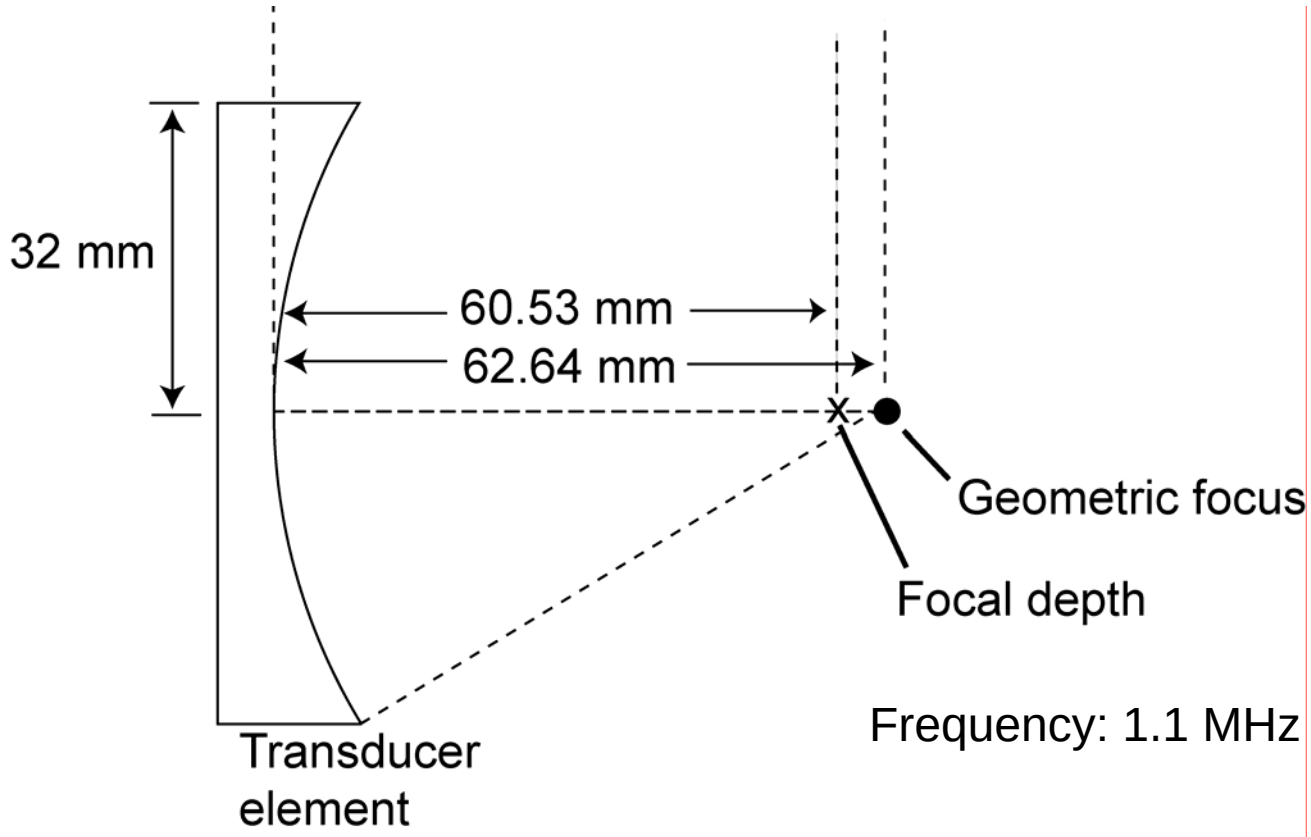
$$I = \frac{120}{3R_{arm} + 3R_{wetcontact} + R_{trunk}}$$

$$= \frac{120}{950}$$

$$= 126 \text{ mA}$$

Example 2

High intensity focused ultrasound transducer



High Intensity Focused Ultrasound Transducer

Sound from a point source

$$\frac{\partial^2 \Phi}{\partial t^2} = c^2 \nabla^2 \Phi$$

Wave equations of sound

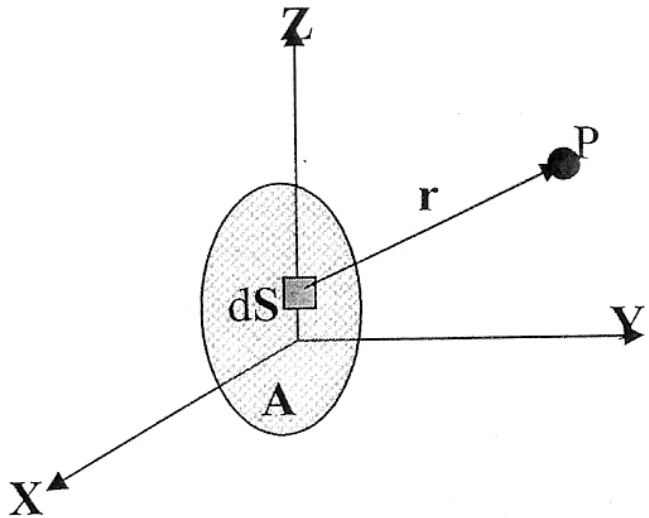
$$u = \nabla \Phi$$

$$p = \rho c u$$

$$u = u_0 e^{j(wt - kr)}$$

c : sound velocity
Φ : velocity potential
u : particle velocity
p : pressure
ρ : density

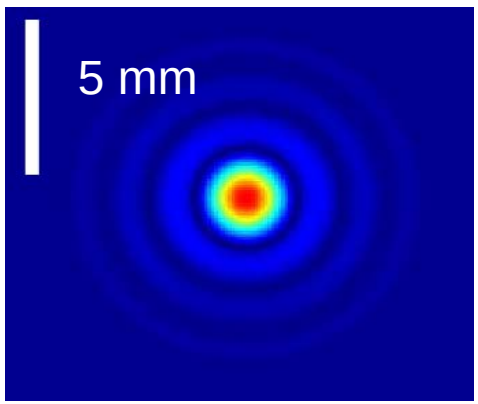
Rayleigh- Sommerfold integral

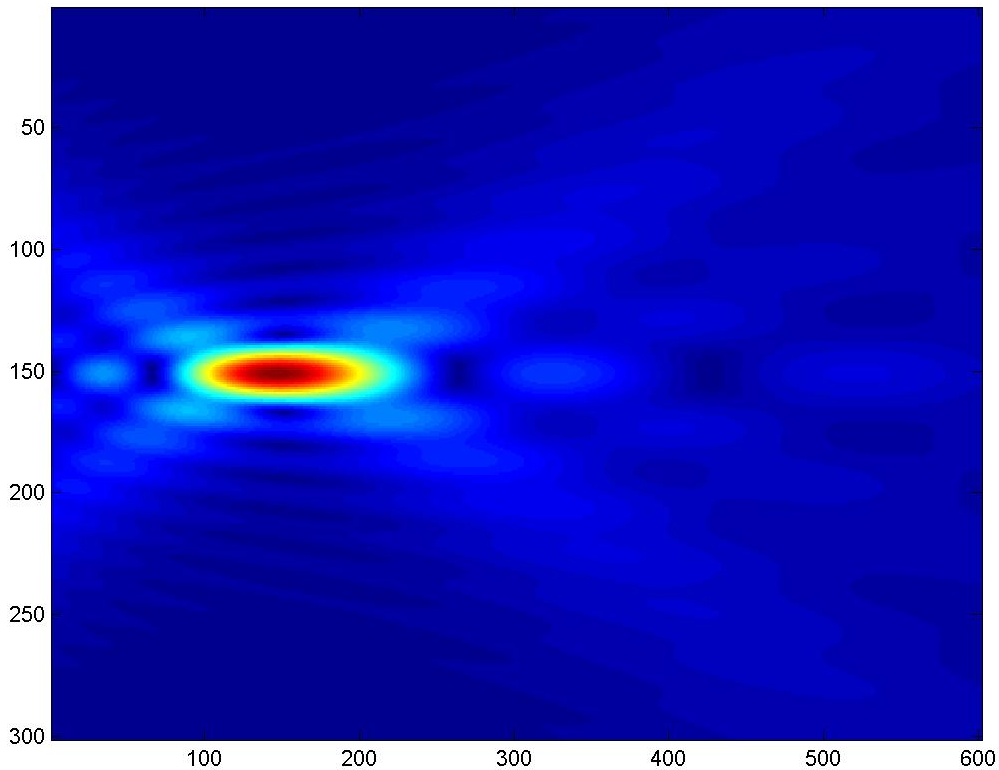


k : Wave number

$$p(x,y,z) = j\frac{\rho c k}{2\pi}\iint_A \frac{u_0 e^{j(wt-kr)}}{r} dS$$

$$p(x,y,z) = j\frac{\rho c k}{2\pi}\sum_m^M \sum_n^N \frac{u_{mn} e^{j(wt-kr)}}{r} \Delta S_{mn}$$



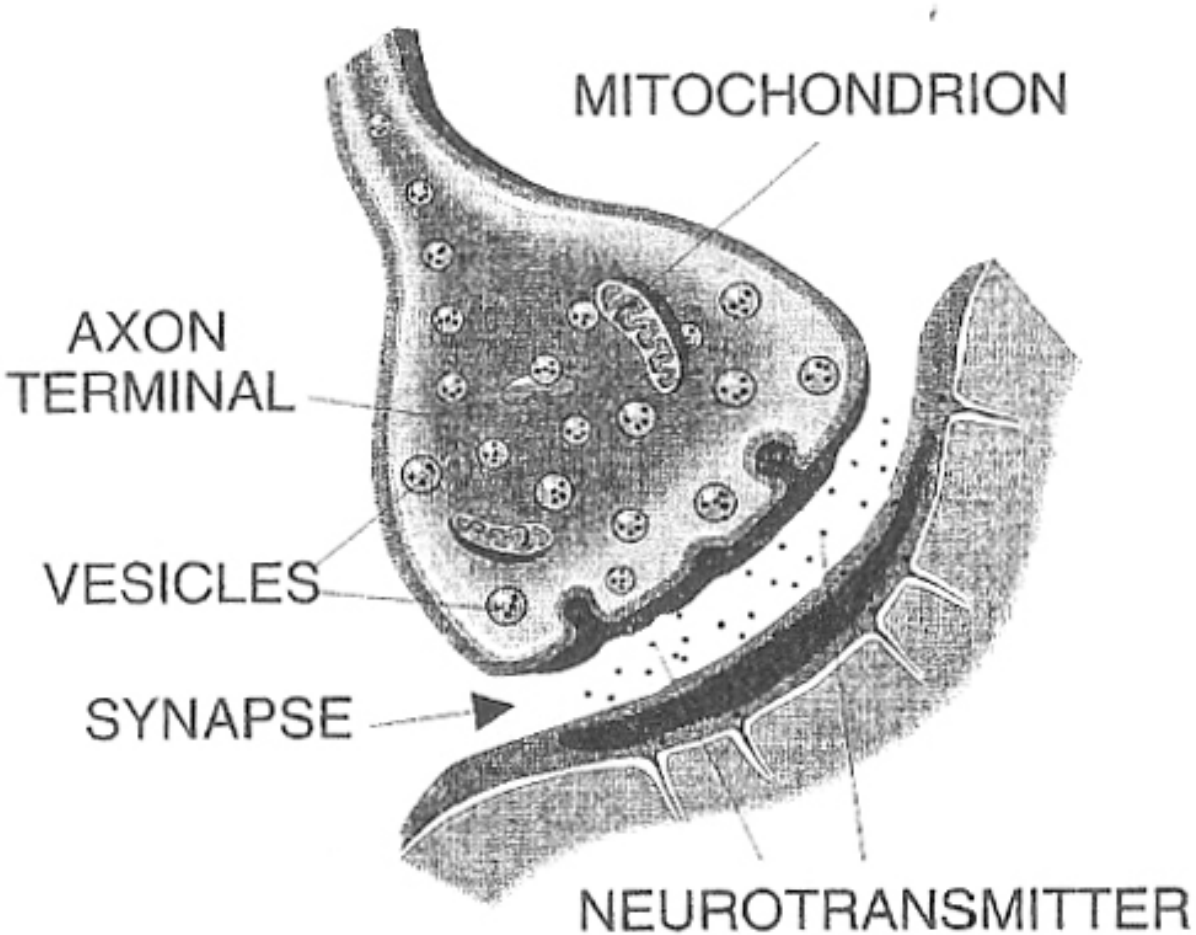


Use Matlab

Qualitative Modeling

Inverse solution

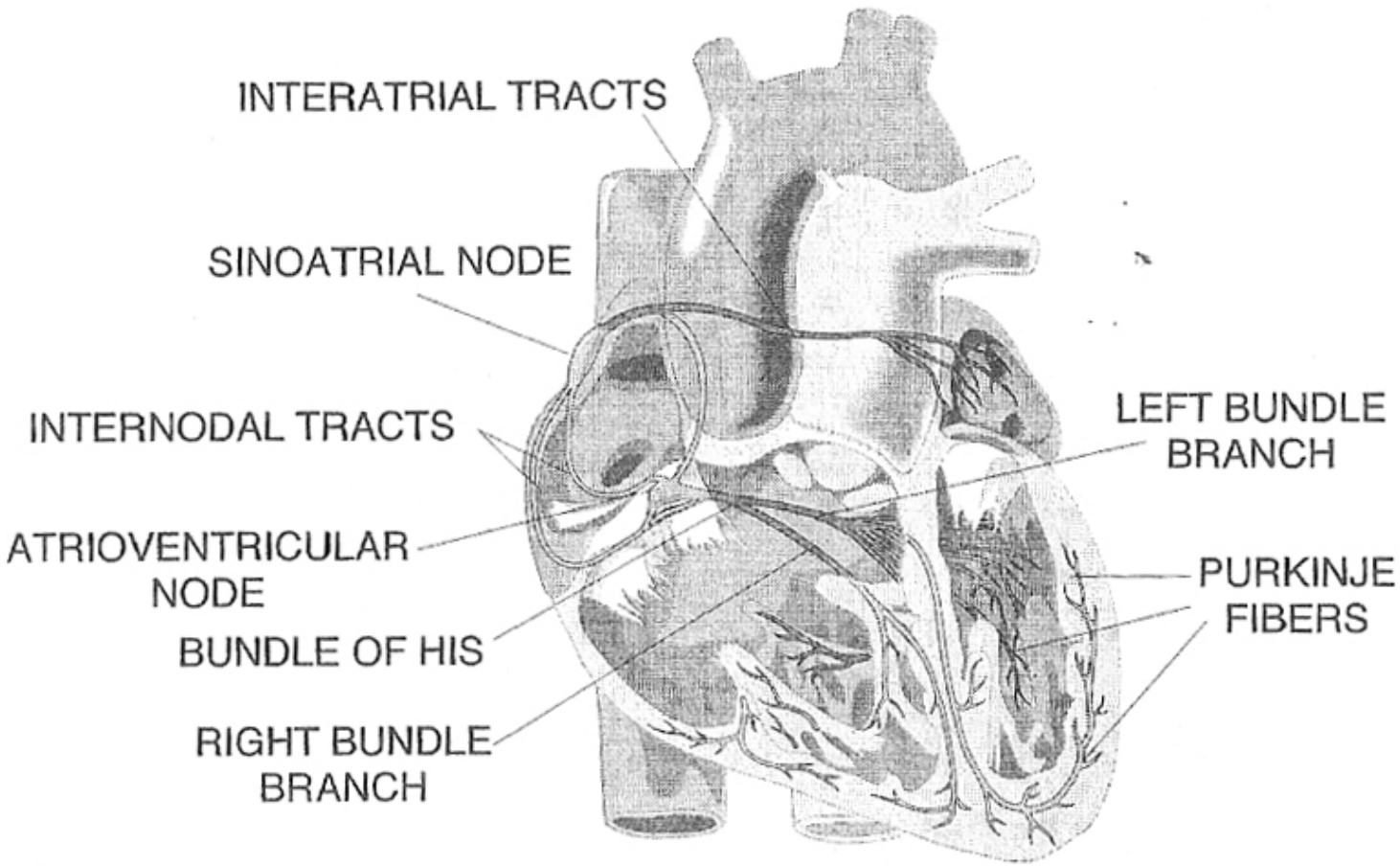
Example 3


MITOCHONDRION
AXON TERMINAL
VESICLES
SYNAPSE
NEUROTRANSMITTER

The Development of the Synapse Model

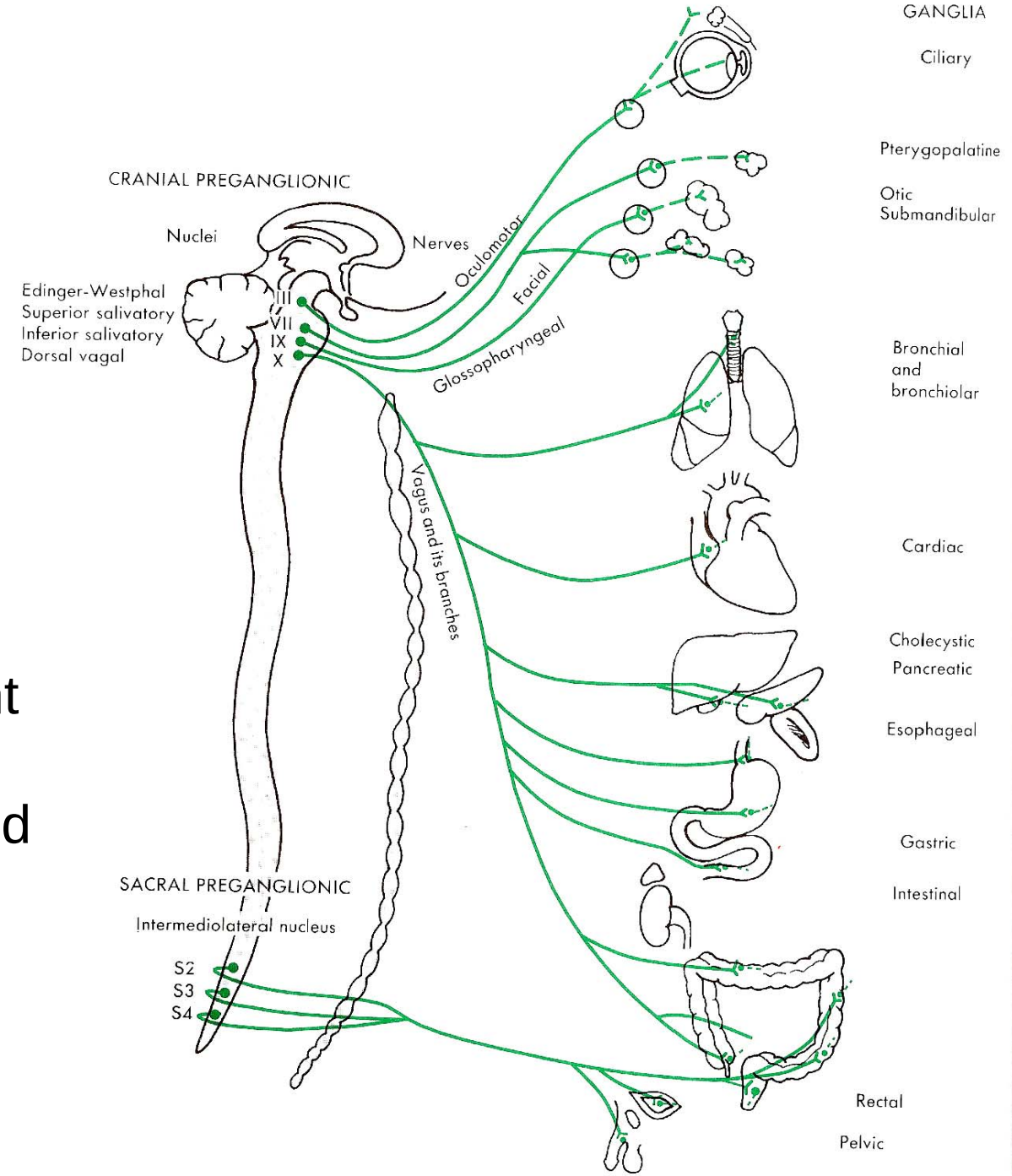
- A black box
- Cell theory vs. syncytium (interconnected by protoplasmic bridges)
- 1843, Du Bois-Reymond: Flow of electric current is involved in both muscle contraction and nerve conduction
- Electrical and chemical transmission
  - Rapid

Conductive system of the heart



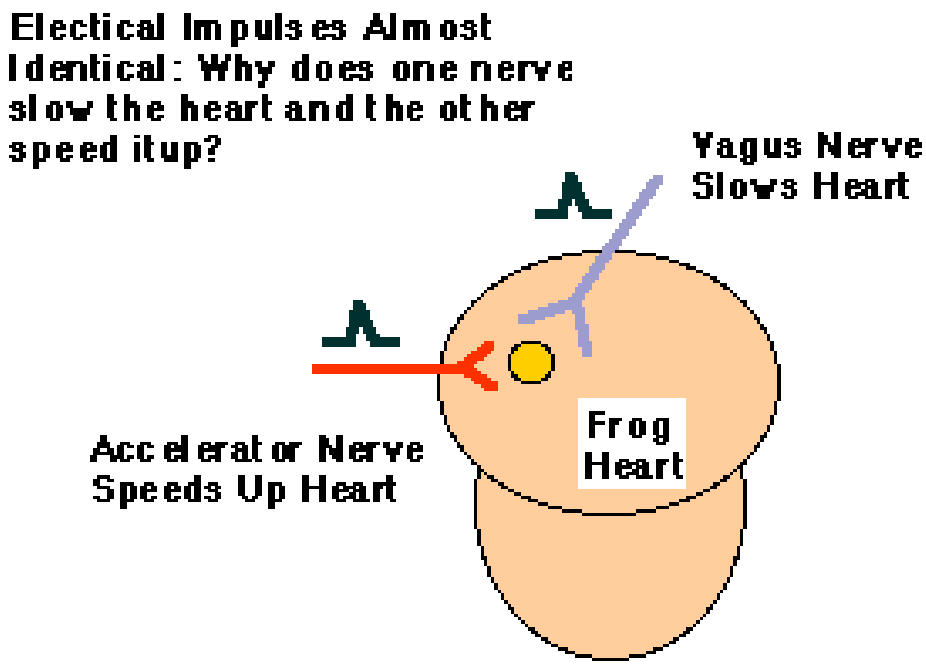
Parasympathetic nervous system

1921, Otto Loewi's frog heart experiment (Vagus n.)
1936, Dale's ACh and muscle contraction

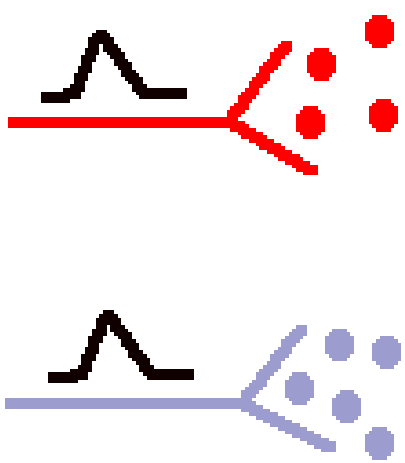


Otto Loewi's Frog Heart Experiments

- **The Problem**:
  - In 1903 Otto Loewi wondered why one of the heart nerves (the accelerator) speeds up the heart and the other (the vagus) slows it down, even though the electrical pulses of the nerves were nearly identical.



- **The Hypothesis:**
  - Loewi suggested that the 2 nerves released different chemicals at their terminals when stimulated. The vagus chemical would slow down the heart and the accelerator chemical would speed it up.

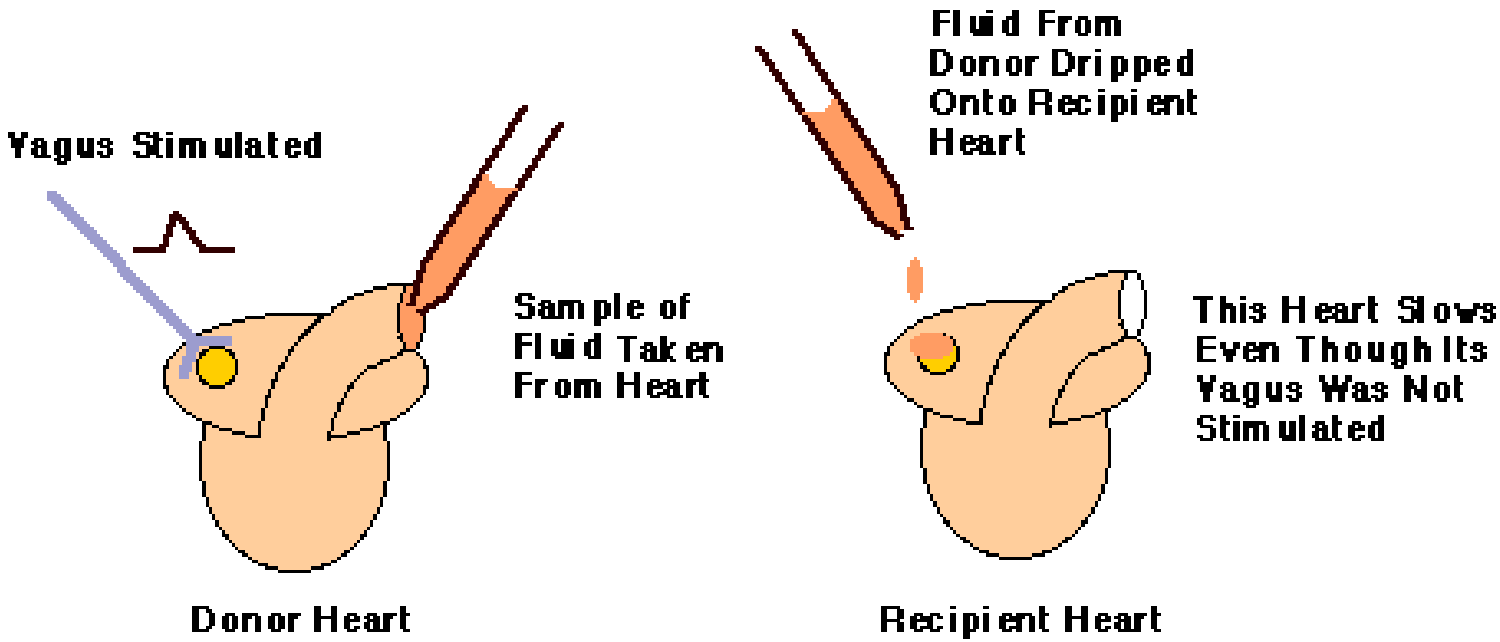


Loewi's Hypothesis:

When stimulated accelerator nerve releases chemical which speads up heart rate

When stimulated vagus nerve releases chemical which slows down heart rate

- **The Experimental Test**
  - 17 years later Loewi had a very strange dream in which a way of testing his hypothesis appeared. He woke up and wrote down some notes, but the next morning he could not read his scribbles! Luckily for him the dream reoccurred the next night and he immediately got up (3AM) and did the experiment.
  - Hearts, with their nerves intact, were dissected from 2 frogs. The hearts were hooked up to mechanical devices which recorded their heart beats. Then the vagus nerve of one heart (the donor) was electrically stimulated. The donor heart immediately slowed down, as expected. A sample of the fluid passing through the donor heart was taken with a small pipette and this fluid was dripped onto the second heart (the recipient). The recipient heart slowed down, even though its vagus had not been stimulated.



- Chemicals (Neurotransmitter) released by the donor heart into the fluid were sufficient to produce slowing.
- The chemical released by the vagus nerve is acetylcholine and the chemical released by the accelerator nerve is noradrenaline.

Sir Henry Dale's Findings

- acetylcholine is also a neurotransmitter in the neuromotor synapse, and that preganglionic synapses in the ANS are all cholinergic, in contrast with the postganglionic ones, which can be either cholinergic or adrenergic.
- Dale also was the first to isolate acetylcholine from mammalian organs.

The Nobel Prize in Physiology or Medicine 1936

"for their discoveries relating to chemical transmission of nerve impulses"

Sir Henry Hallett Dale

1/2 of the prize

United Kingdom

National Institute for Medical Research
London, United Kingdom

b. 1875
d. 1968

Otto Loewi

1/2 of the prize

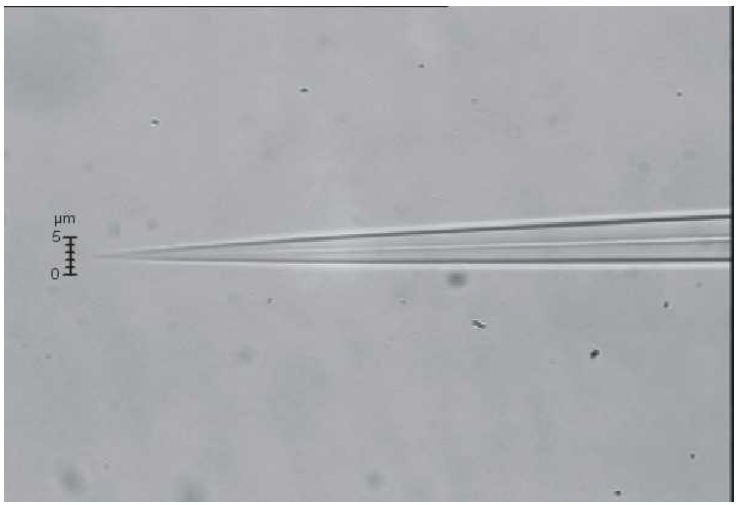
Austria

Graz University
Graz, Austria

b. 1873
(in Frankfurt-on-the-Main, Germany)
d. 1961

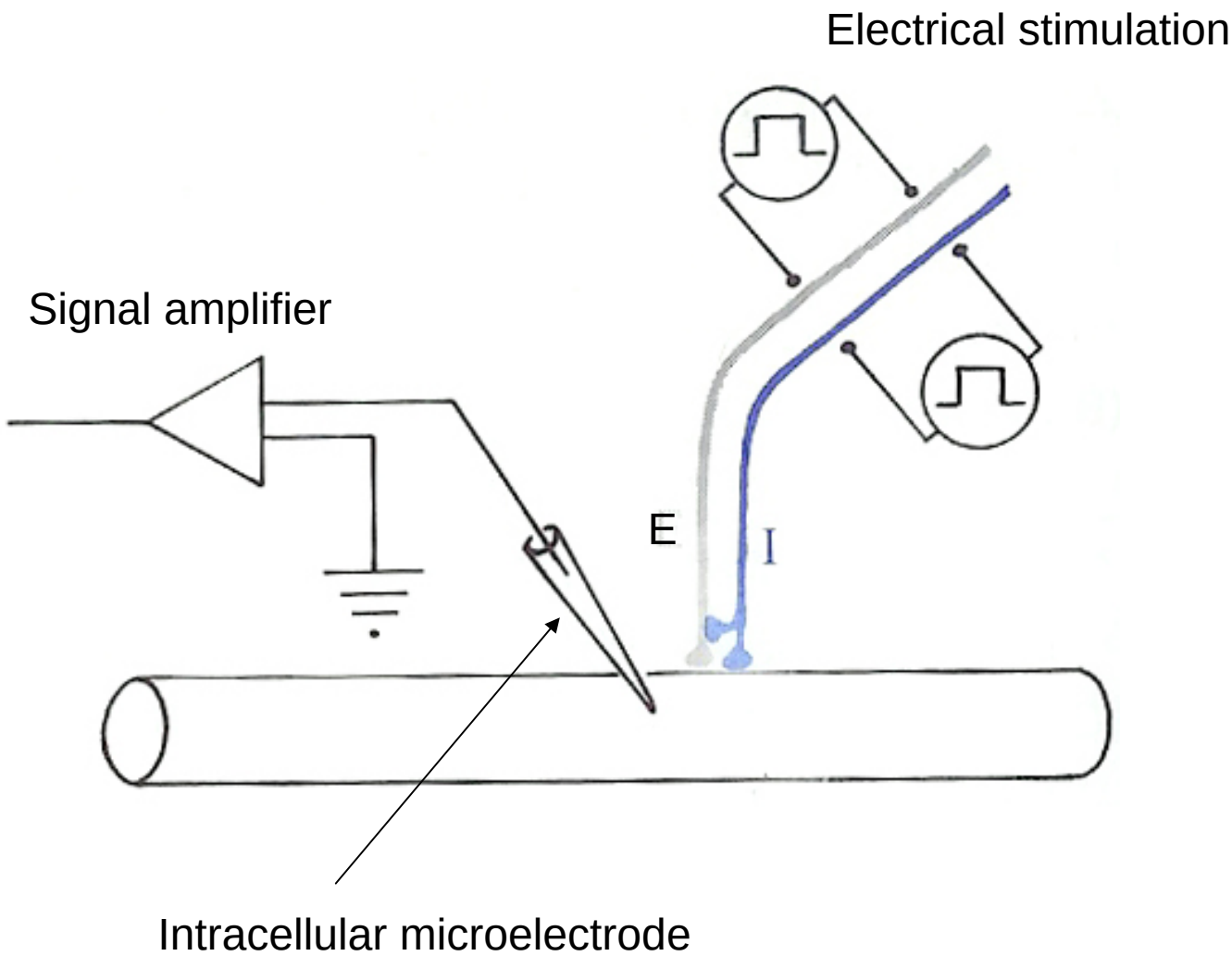
Chemical Synaptic Transmission

- Nerve terminal: button
- Synaptic cleft: 30 nm in distance
- Exocytosis and synpatic vesicles
- Acethycholine (ACh) neurotransmitter
- Motor end plate
- ACh receptors
- Acetylcholinesterase – hydrolyze ACh



Ultrafine tipped glass microelectrode is filled with conducting fluid. The scale is 5 micrometers.

A glass micropipette puller apparatus


Electrical stimulation
Signal amplifier
E
I
Intracellular microelectrode

The Nobel Prize in Physiology or Medicine 1963

"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

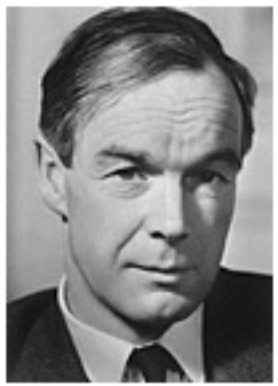
Sir John Carew Eccles

1/3 of the prize

Australia

Australian National University
Canberra, Australia

b. 1903
d. 1997



Alan Lloyd Hodgkin

1/3 of the prize

United Kingdom

University of Cambridge
Cambridge, United Kingdom

b. 1914
d. 1998

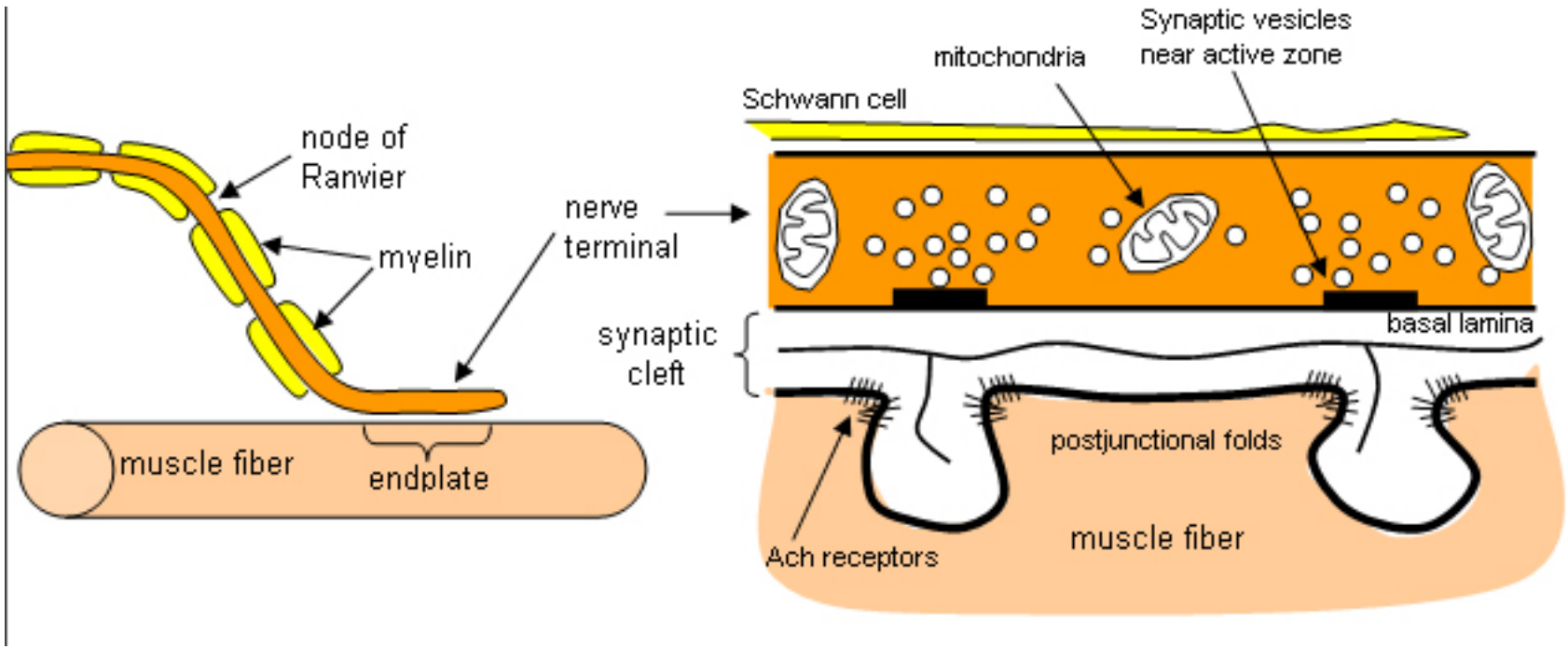
Andrew Fielding Huxley

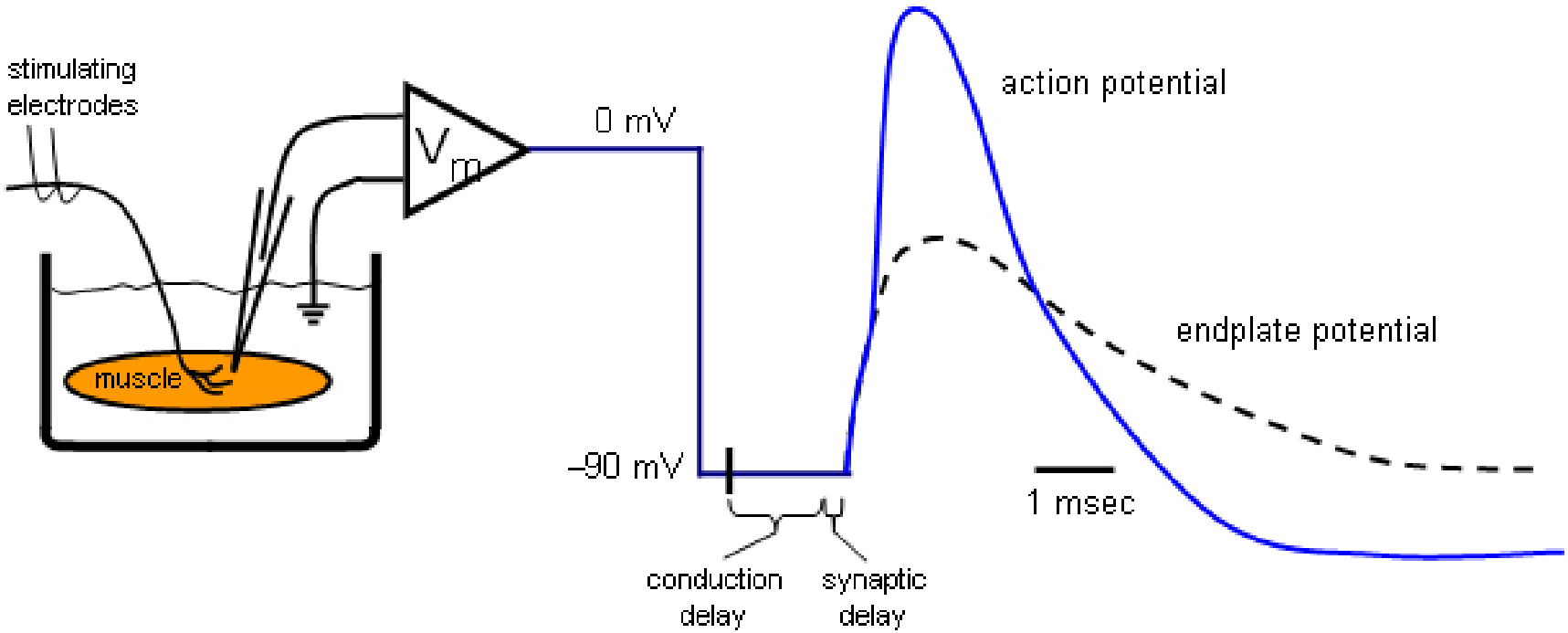
1/3 of the prize

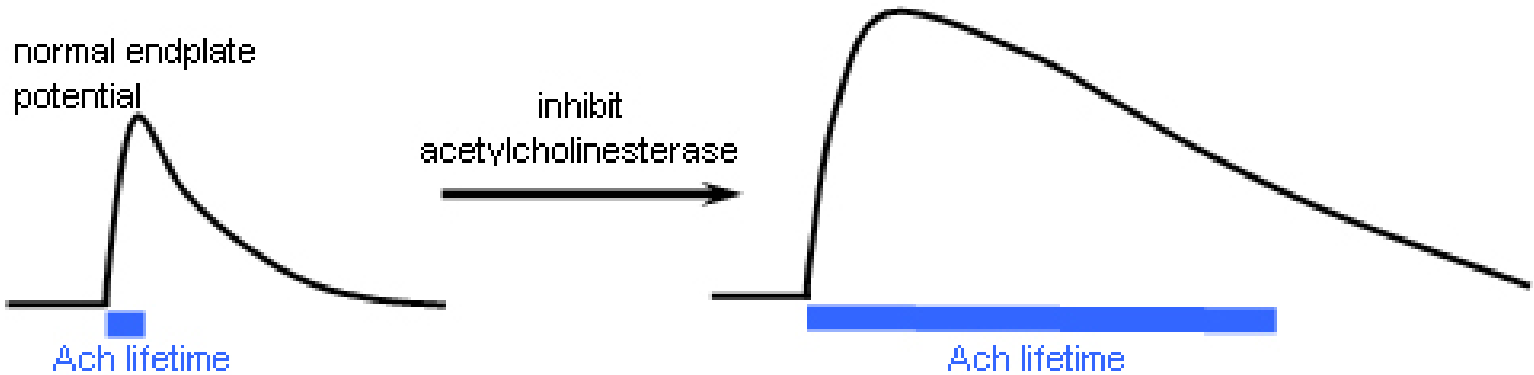
United Kingdom

London University
London, United Kingdom

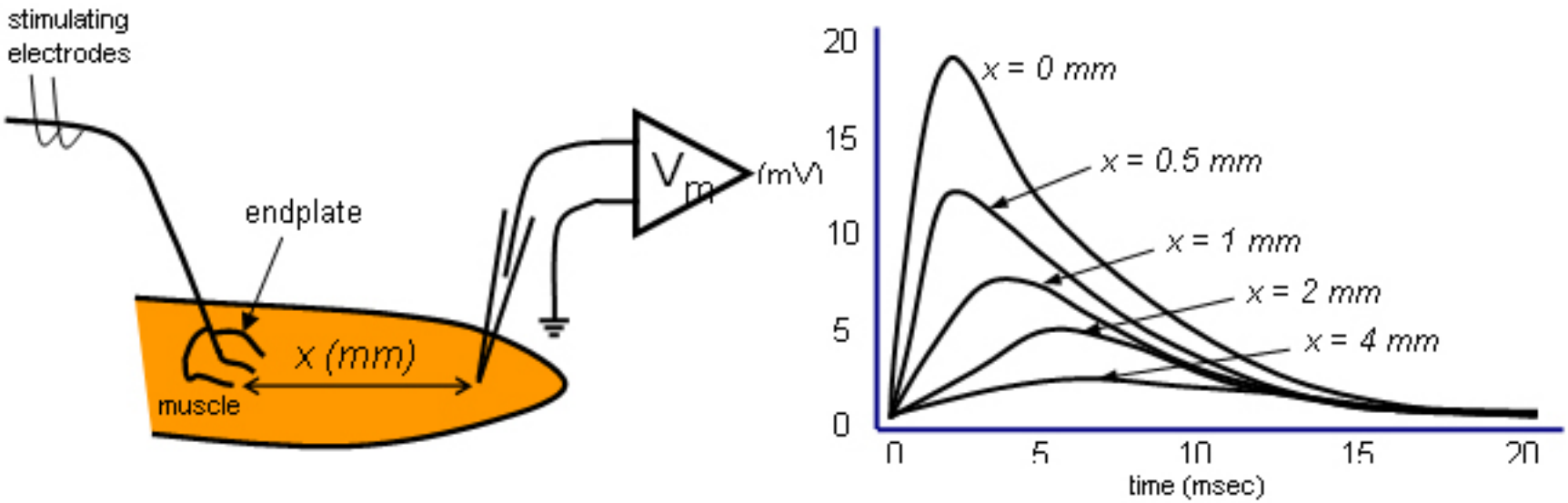
b. 1917


node of
Ranvier
myelin
nerve
terminal
muscle fiber
endplate
Schwann cell
mitochondria
Synaptic vesicles
near active zone
synaptic
cleft
basal lamina
postjunctional folds
muscle fiber
Ach receptors

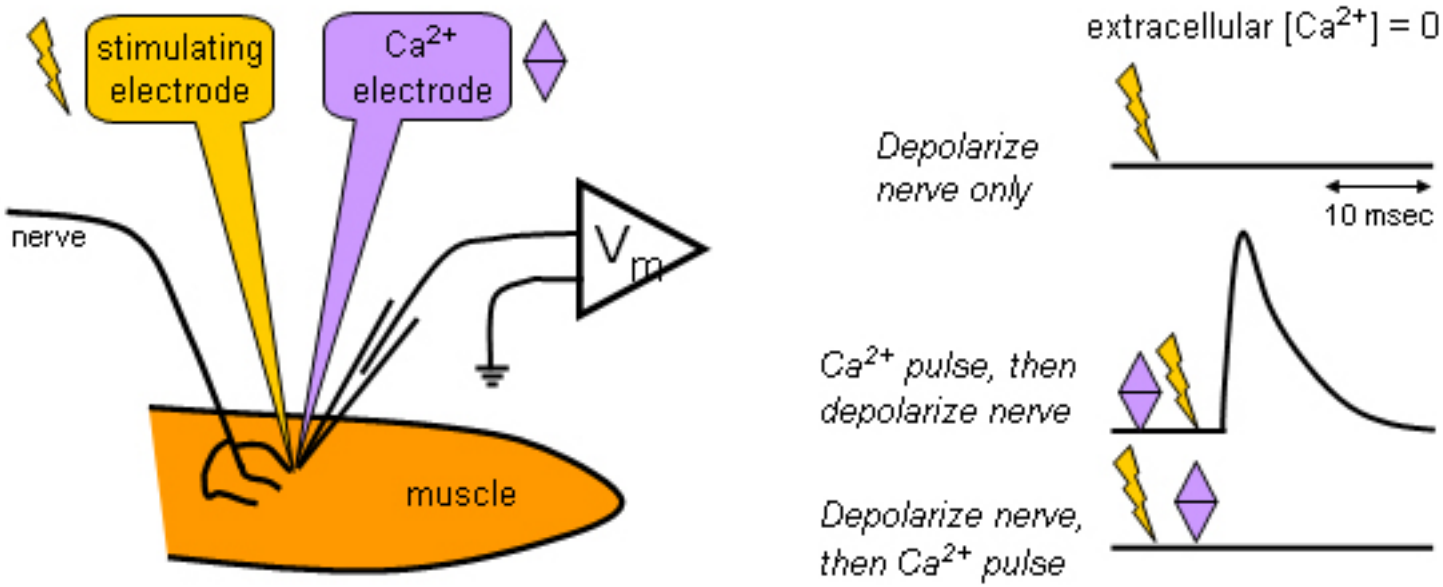

stimulating
electrodes
muscle
V
m
0 mV
–90 mV
action potential
endplate potential
1 msec
conduction
delay
synaptic
delay



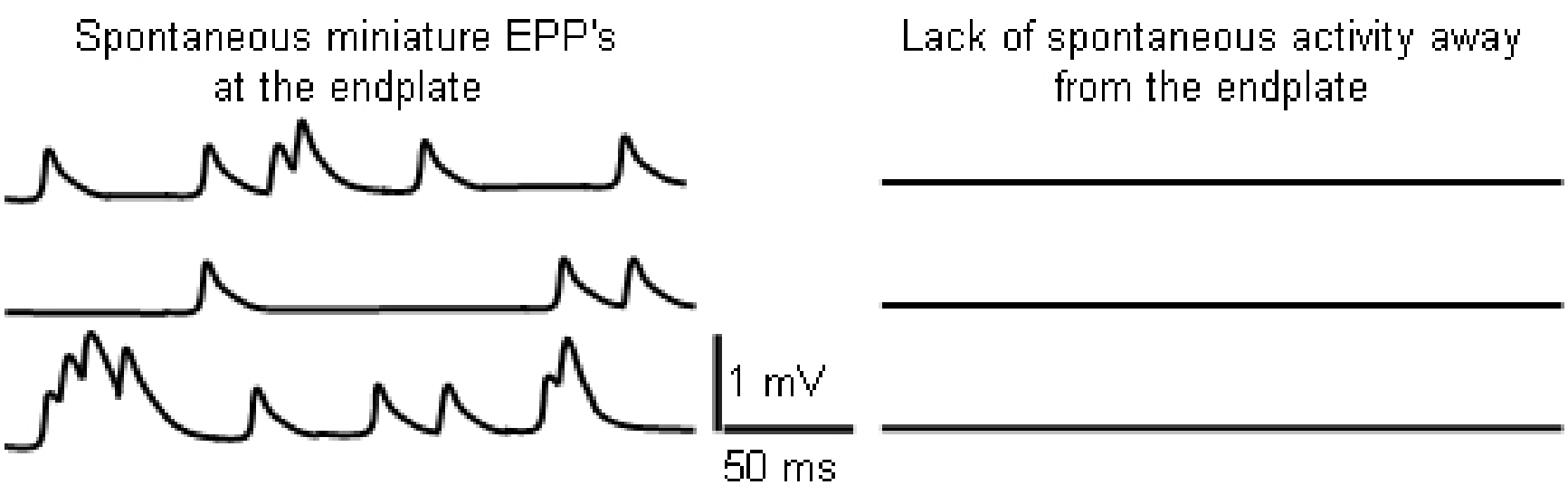
The lifetime of Ach in the synaptic cleft is brief
*Inhibitor: Neostigmine



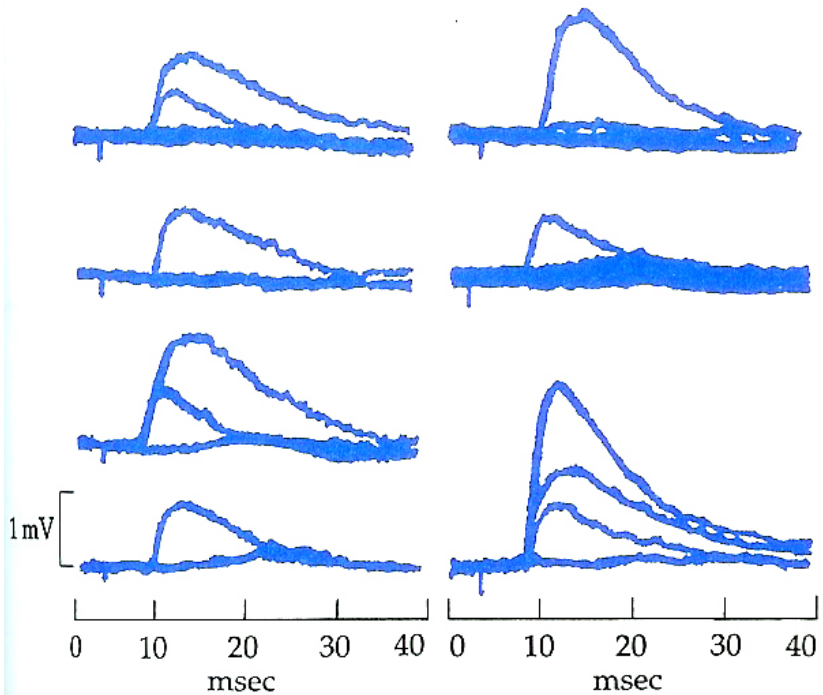
Spatial decay of the EPP is a passive process determined by the cable properties of the muscle fiber



The Ca^{+2} -dependence of Ach release.


Spontaneous miniature EPP's
at the endplate
Lack of spontaneous activity away
from the endplate
1 mV
50 ms

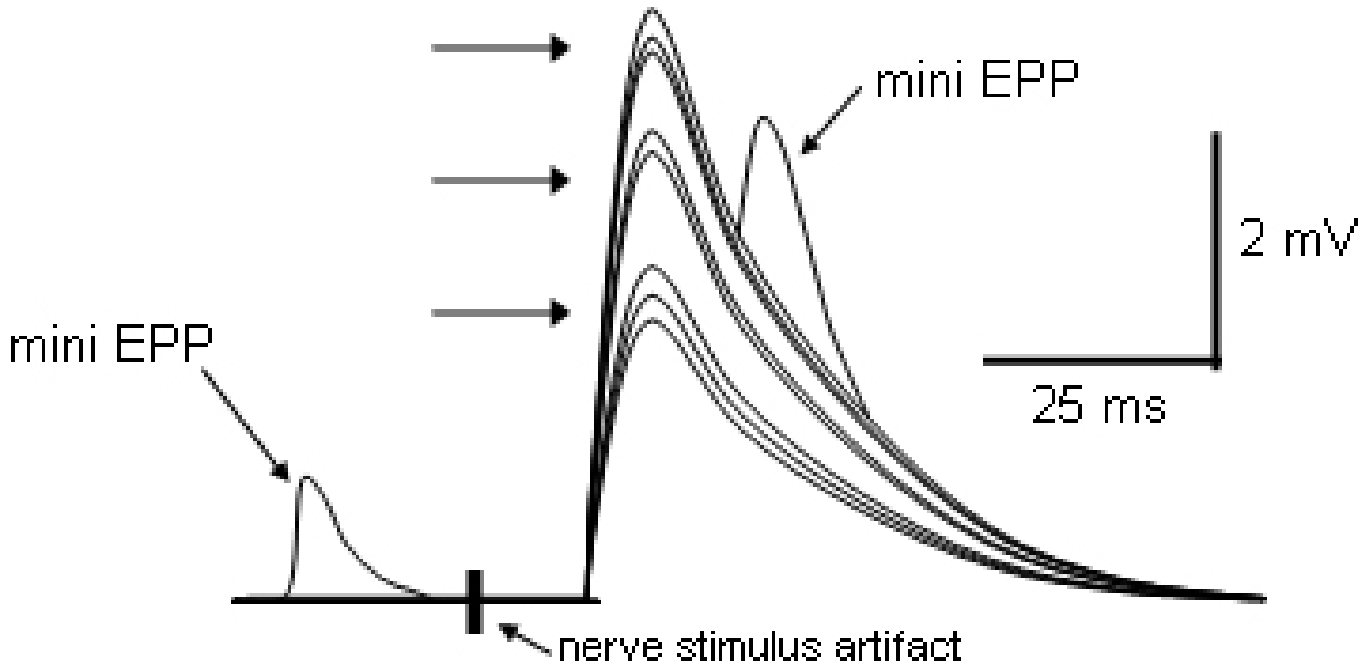
Quantum Hypothesis



18

FLUCTUATIONS IN SYNAPTIC RESPONSE at a neuromuscular junction. Presynaptic release of ACh was reduced by reducing the extracellular calcium concentration in the bathing solution. Each set of traces shows two to four superimposed responses to nerve stimulation. Stepwise fluctuations in amplitude are due to variations in the number of quanta of ACh released on successive trials. (From Fatt and Katz, 1952.)

Calcium → transmitter release
Reduce calcium concentration



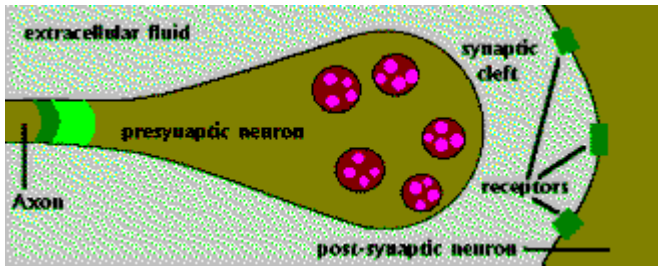
Quantal fluctuations of nerve-evoked EPP's. Eight examples of EPPs are superimposed. It can be seen that their amplitudes cluster around three distinct levels marked by horizontal arrows. The separation between each level is approximately equal to the amplitude of the spontaneous mini EPP.

ACh alone cannot induce the mini EPP responses.

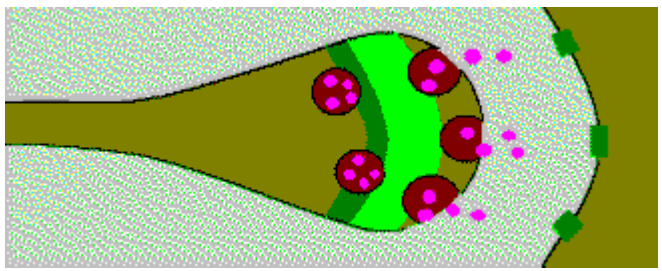
Synapse Transmission

- Action potential → presynaptic depolarization → calcium entry → transmitter release → postsynaptic depolarization → action potential
- Neurotransmitter : Acetylcholine (ACh)
- Quantum release
- Quantum number varied, but the quantum size (ACh molecules in each quantum) fixed

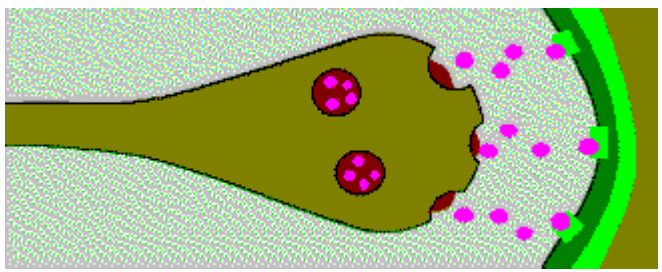
Current Synapse model



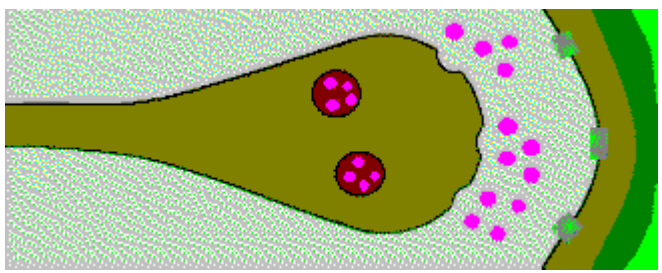
Step 1. The neurotransmitter is manufactured by the neuron and stored in vesicles at the axon terminal.



Step 2. When the action potential reaches the axon terminal, it causes the vesicles to release the neurotransmitter molecules into the synaptic cleft.



Step 3. The neurotransmitter diffuses across the cleft and binds to receptors on the post-synaptic cell.



Step 4. The activated receptors cause changes in the activity of the post-synaptic neuron.

The Nobel Prize in Physiology or Medicine 1970

"for their discoveries concerning the humoral transmittors in the nerve terminals and the mechanism for their storage, release and inactivation"

Sir Bernard Katz

1/3 of the prize

United Kingdom

University College London, United Kingdom

b. 1911
d. 2003

Ulf von Euler

1/3 of the prize

Sweden

Karolinska Institutet
Stockholm, Sweden

b. 1905
d. 1983

Julius Axelrod

1/3 of the prize

USA

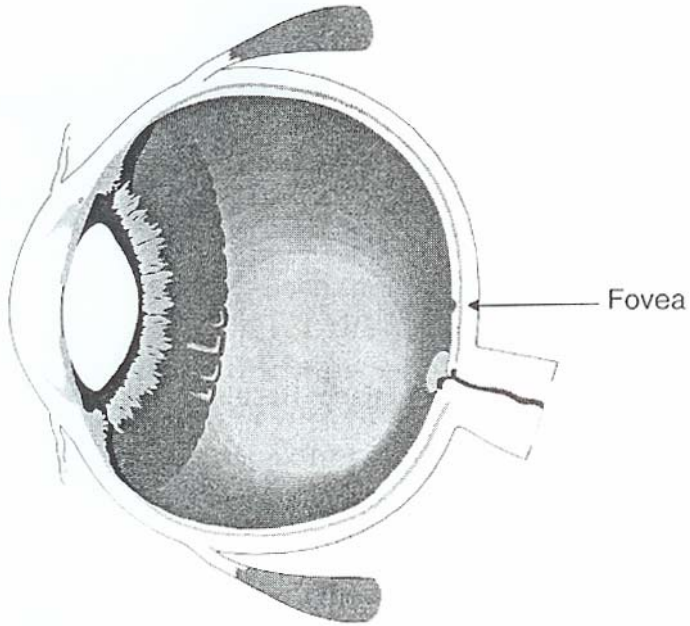
National Institutes of Health
Bethesda, MD, USA

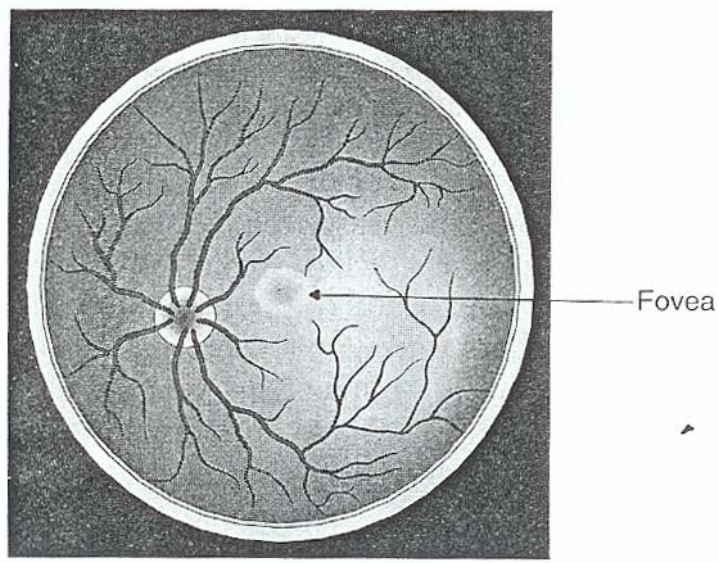
b. 1912
d. 2004

Quantitative Modeling

Inverse solution

Example 4





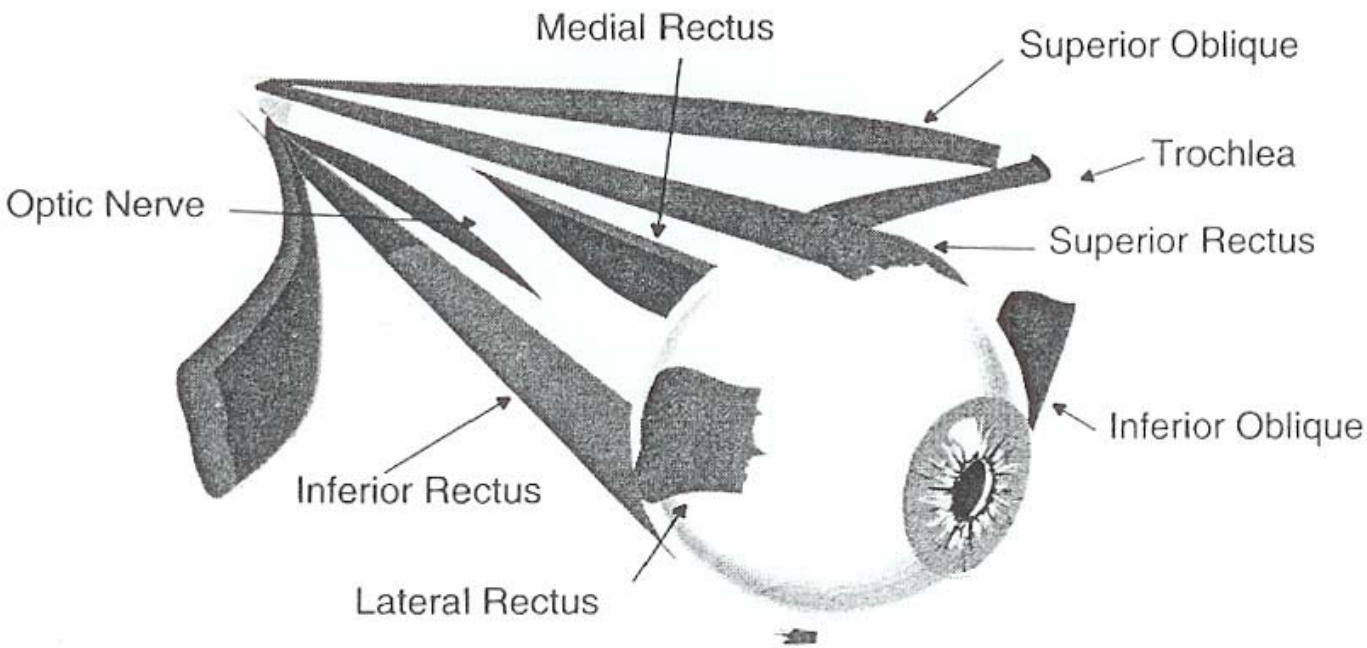
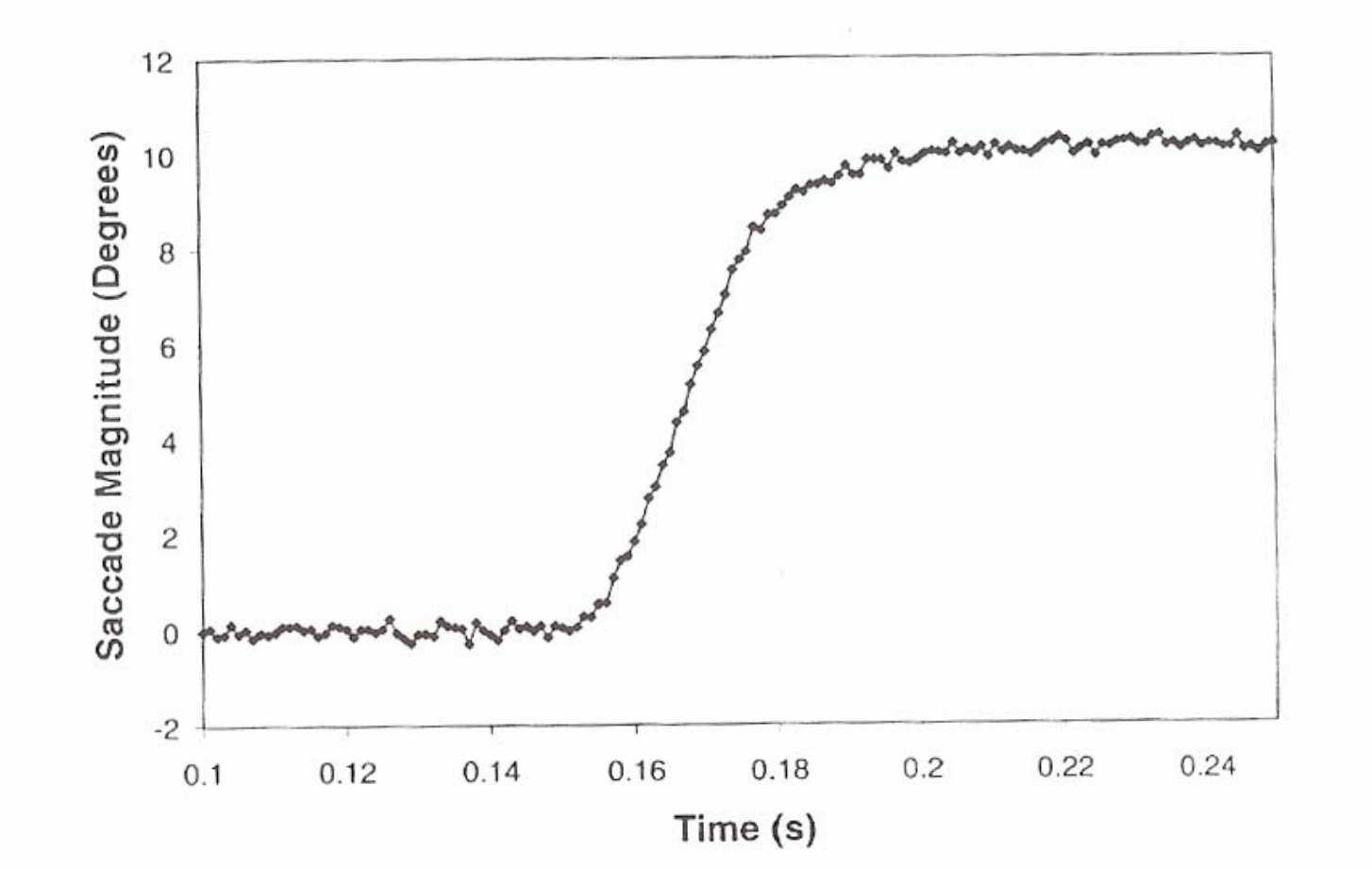
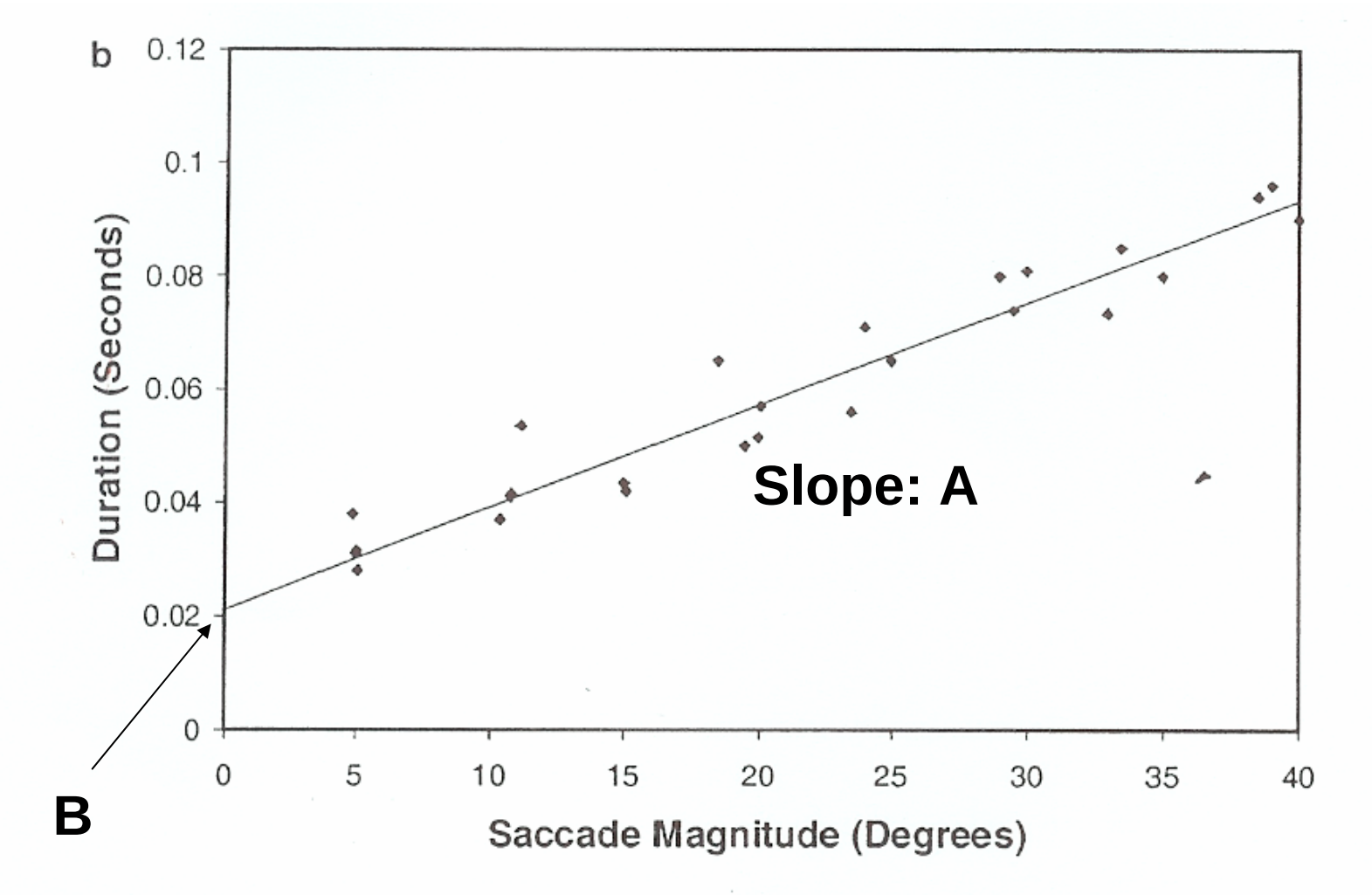


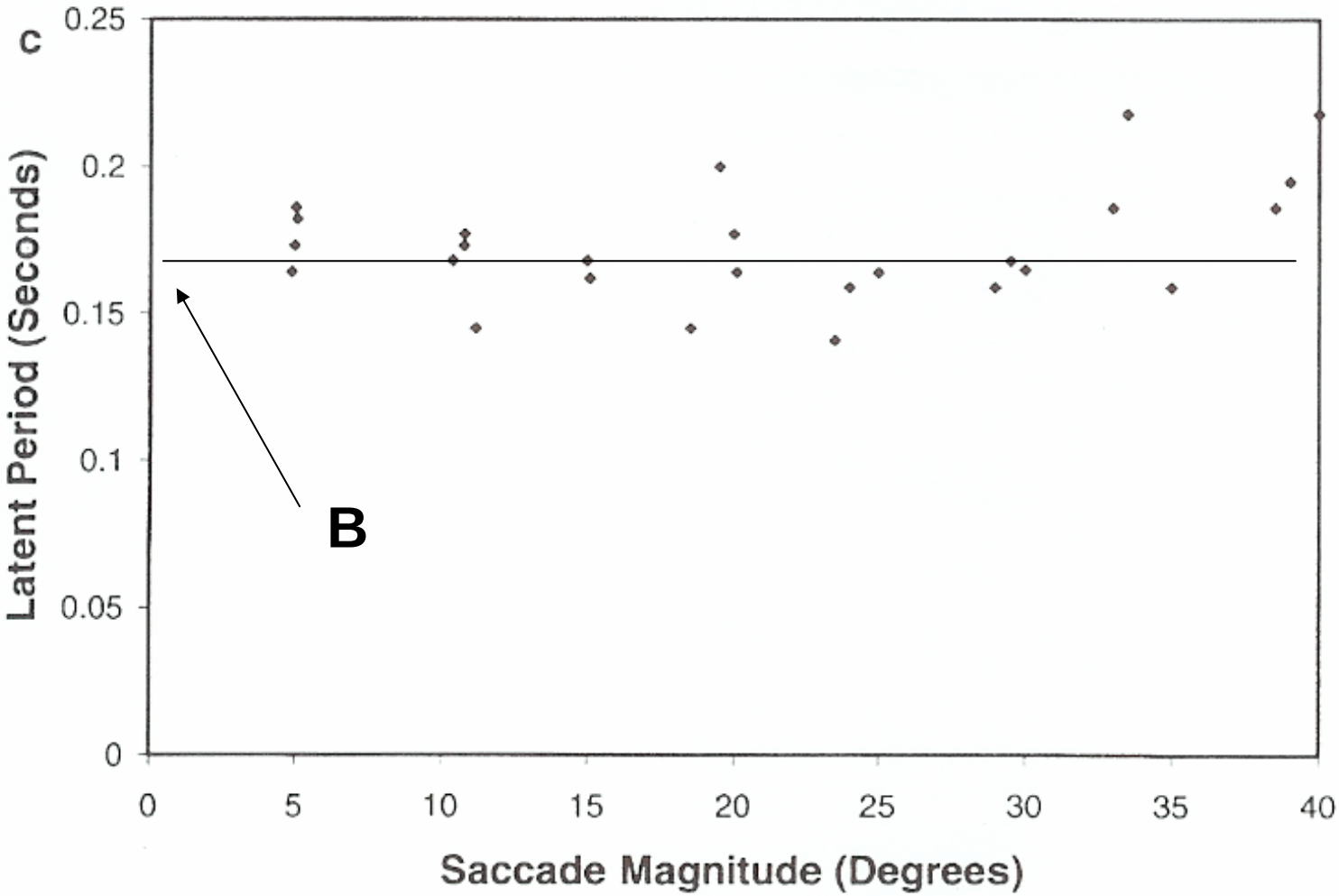
Fig. 7.2 Diagram illustrating the muscles and optic nerve of the right eye. The left eye is similar except the lateral and medial rectus muscles are reversed. The lateral and medial rectus muscles are used to move the eyes in a horizontal motion. The superior rectus, inferior rectus, superior oblique, and inferior oblique are used to move the eyes vertically and torsionally. The contribution from each muscle depends on the position of the eye. When the eyes are looking straight ahead, called primary position, the muscles are stimulated and under tension.

Saccade Amplitude vs. Time



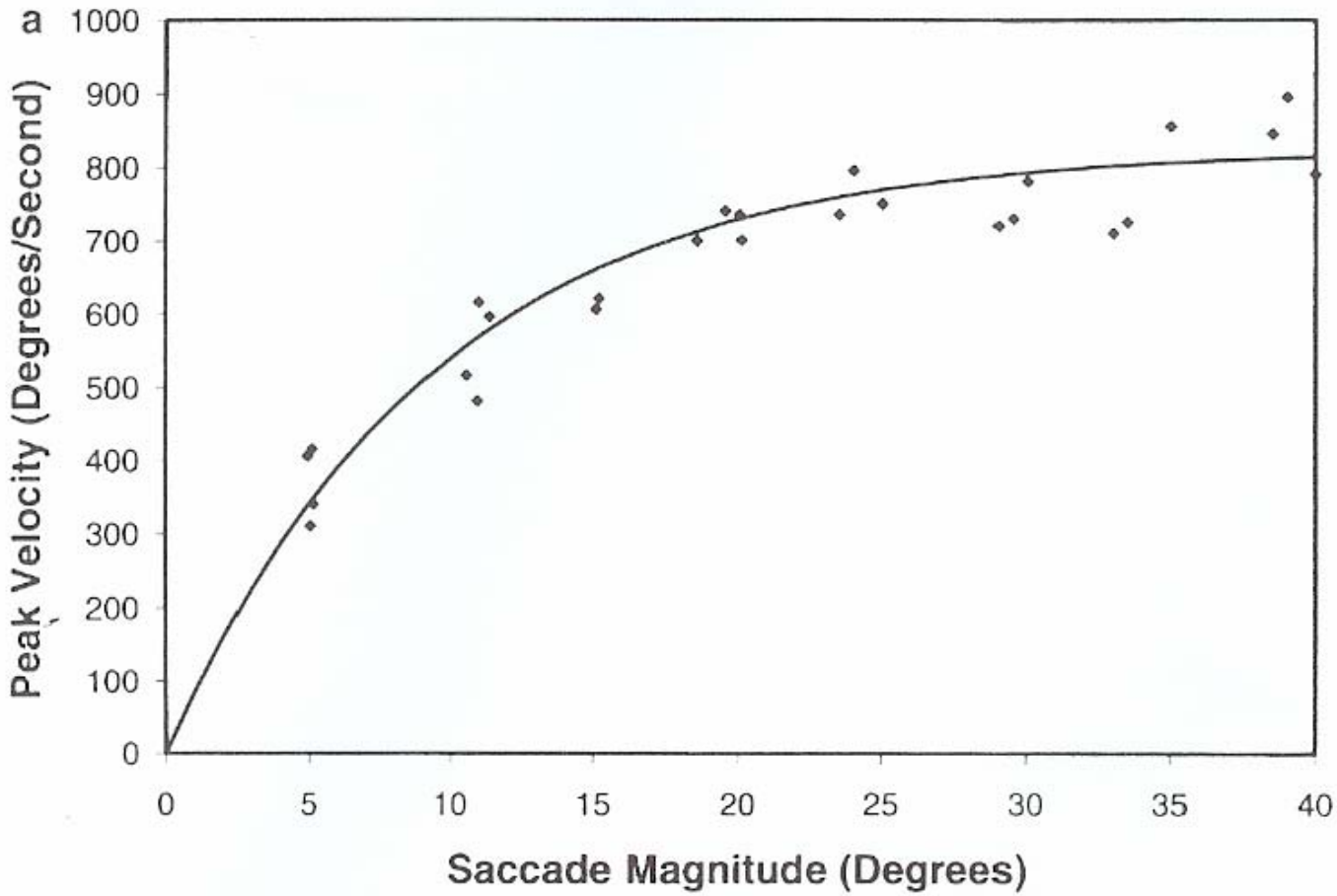


Duration = A*(Saccade Magnitude)+B



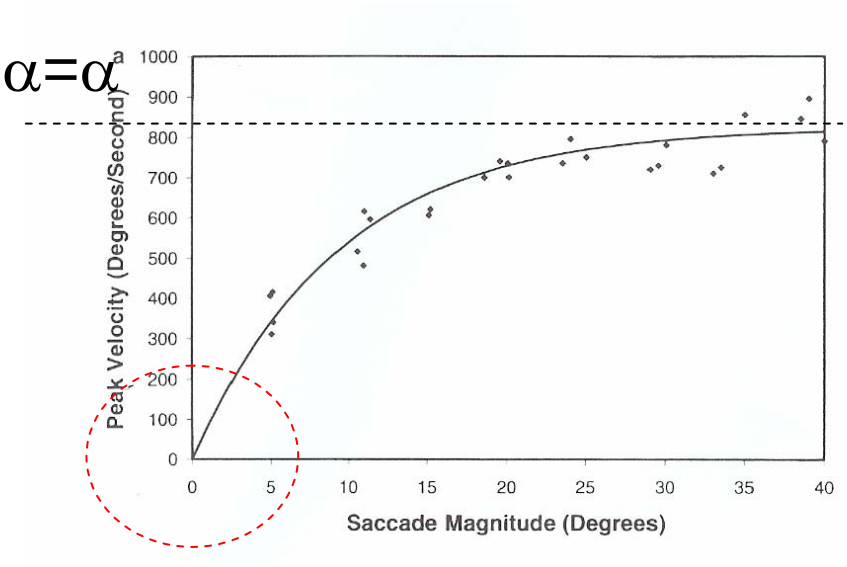
Latent Period = B

Saccade Magnitude vs. Peak Velocity



Saturation model

$$V = V_0 + \alpha(1 - e^{-\frac{x}{\beta}})$$



V : maximal velocity

V_0 = 0 (initial velocity)

x : saccade size

α : stead-state peak amplitude (>0)

β : time constant (>0)

$$V = V_0 + \alpha(1 - e^{-\frac{x}{\beta}})$$

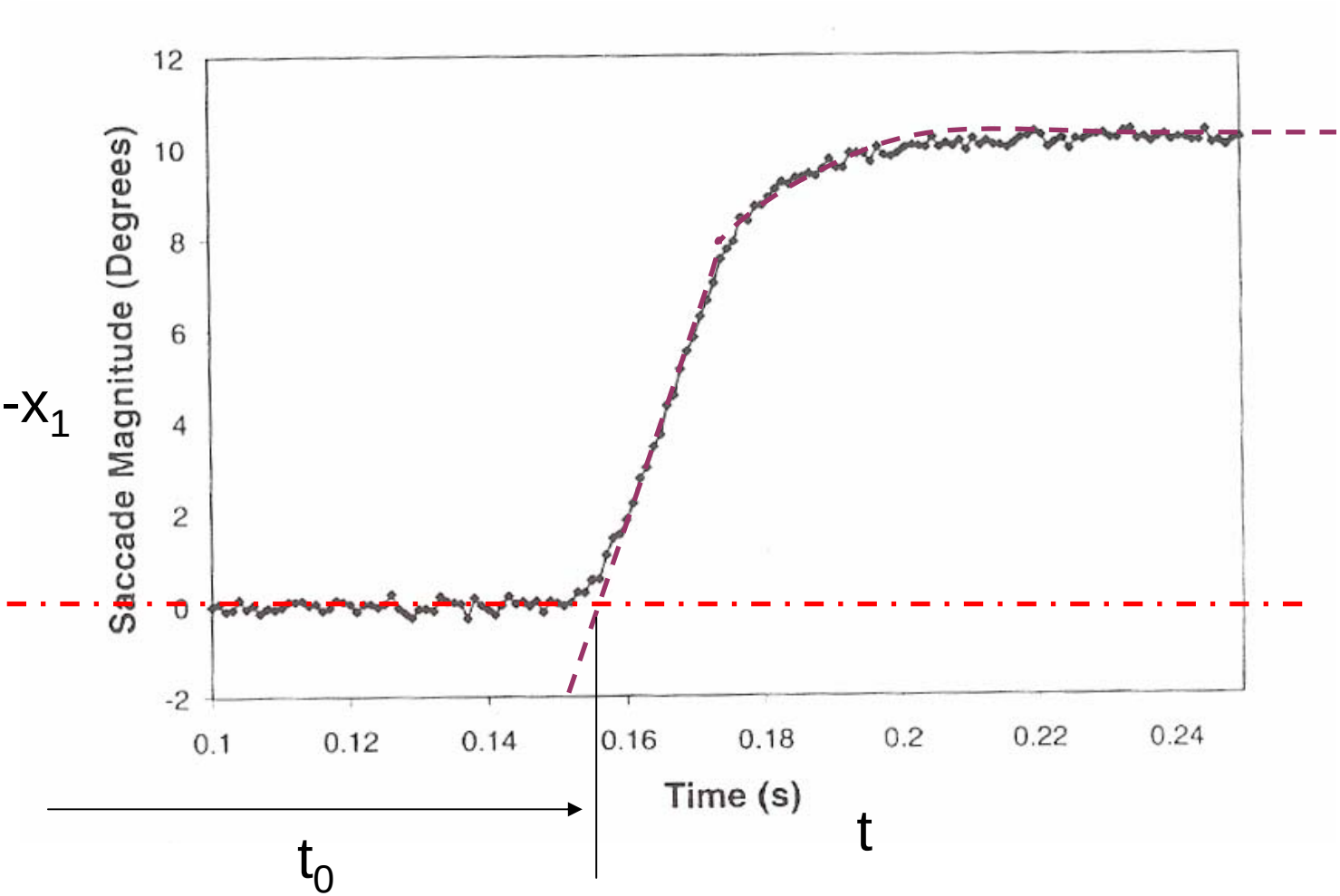
$$= (V_0 + \alpha) - \alpha * e^{-\frac{x}{\beta}}$$

$$V' = \frac{\alpha}{\beta} e^{-\frac{x}{\beta}}$$

$$\Rightarrow \beta V(x)' + V(x) - (\alpha + V_0) = 0$$

Saccade Amplitude vs. Time

$x=x_2-x_1$



Inverse approach:

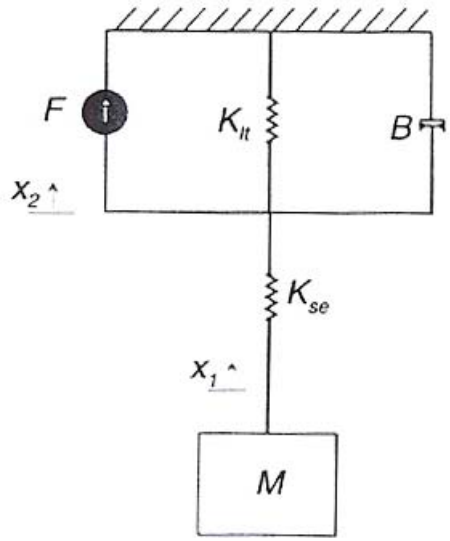
Delay time: t_0

$$x = (x_2 - x_1) = \alpha(1 - e^{-\frac{(t-t_0)}{\beta}})$$

$$\beta\dot{x}(t - t_0) + x(t - t_0) - \alpha = 0$$

A linear first-order system.

To become a system: use Laplace transform to build the transfer function, poles and zeros.



Solution

Assume that $\dot{x}_2 > \dot{x}_1$ and that the mass is supported so that $\dot{x}_1 > 0$. Let the term $K_{st} = K_{se} + K_{lt}$. Summing the forces acting on nodes 1 and 2 gives

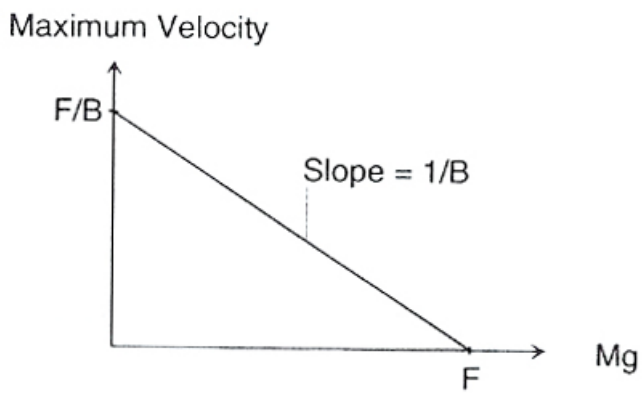
$$Mg = K_{se}(x_2 - x_1) \quad \rightarrow \quad x_1 = x_2 - \frac{Mg}{K_{se}}$$

$$F = B\dot{x}_2 + K_{lt}x_2 + K_{se}(x_2 - x_1)$$

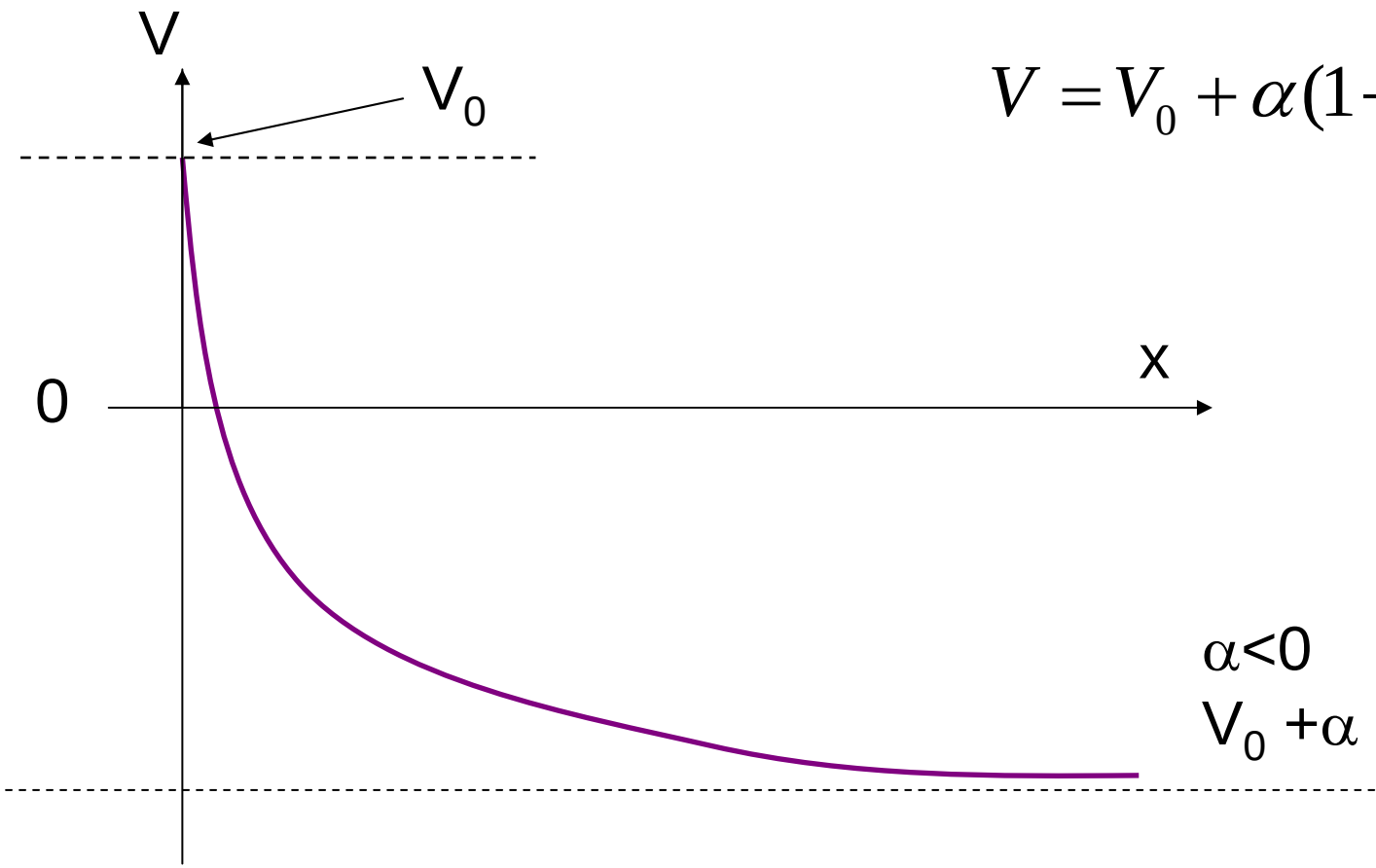
$$x_2(t) = \frac{F - Mg}{K_{lt}} \left(1 - e^{\frac{-K_{lt}t}{B}}\right)$$

$$\dot{x}_2(t) = \frac{F - Mg}{B} e^{\frac{-K_{lt}t}{B}}$$

Maximum velocity, V_{max}, for all loads is given by $V_{max} = \frac{F - Mg}{B}$ and $\dot{x}_1 = \dot{x}_2$ since $\dot{x}_1 = \frac{d}{dt}\left(x_2 - \frac{Mg}{K_{se}}\right)$. The graph depicts a linear relationship between maximum velocity and load.



If α<0, a plot of negative saturation will be depicted.



Exponential increase and decay:

Exponential Growth

If N_0 is the initial population and the growth rate is k then the population N at time t is:

$$N = N_0 e^{kt}, \text{ where } k > 0 \qquad (1)$$

Exponential Decay

If N_0 is the initial population and the decay rate is k then the population N at time t is:

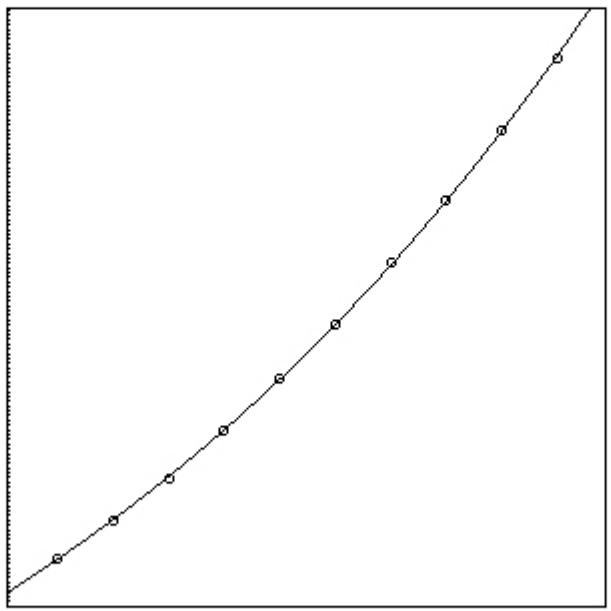
$$N = N_0 e^{kt}, \text{ where } k < 0 \qquad (2)$$

Population growth – exponential growth

During the 1980s the population of a certain city went from 100,000 to 205,000. Populations by year are listed in the table below.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Population in thousands	100	108	117	127	138	149	162	175	190	205

This data is approximated well by the exponential growth model $P = 100\ e^{0.08t}$, where t is the number of years since 1980. In other words, the year 1980 corresponds to $t = 0$, 1981 corresponds to $t = 1$, etc. The data points and model are graphed below.



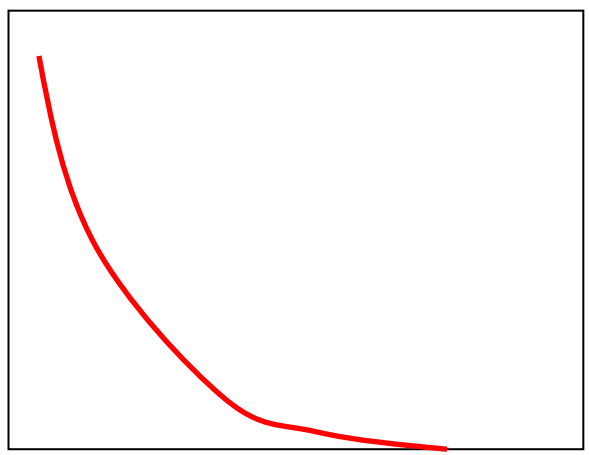
Population data points and model $P = 100\ e^{0.08t}$

where t is number of years since 1980.

Exponential decay

- In a sample of radionuclides or other particles that radioactively decay to a different state, the number of particles in the original state follows exponential decay. See also Radioactive decay.
- If an object at one temperature is exposed to a medium of another temperature, the temperature difference between the object and the medium follows exponential decay.
- The rates of certain types of chemical reactions depend on the concentration of one or another reactant. These reaction rates consequently follow exponential decay. For instance, enzyme-catalyzed reactions behave this way.

Half life: $t_{0.5} = \frac{\ln 2}{-k}$



Oculomotor Model – Passive Elasticity

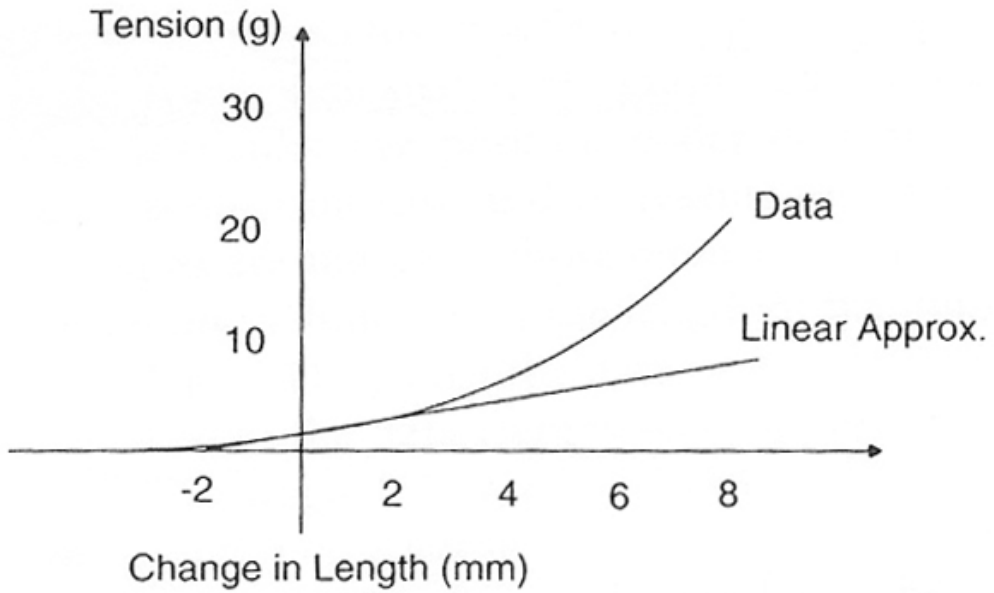
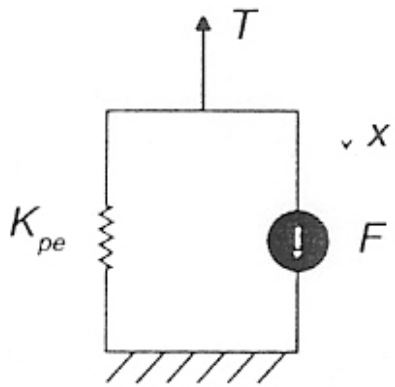
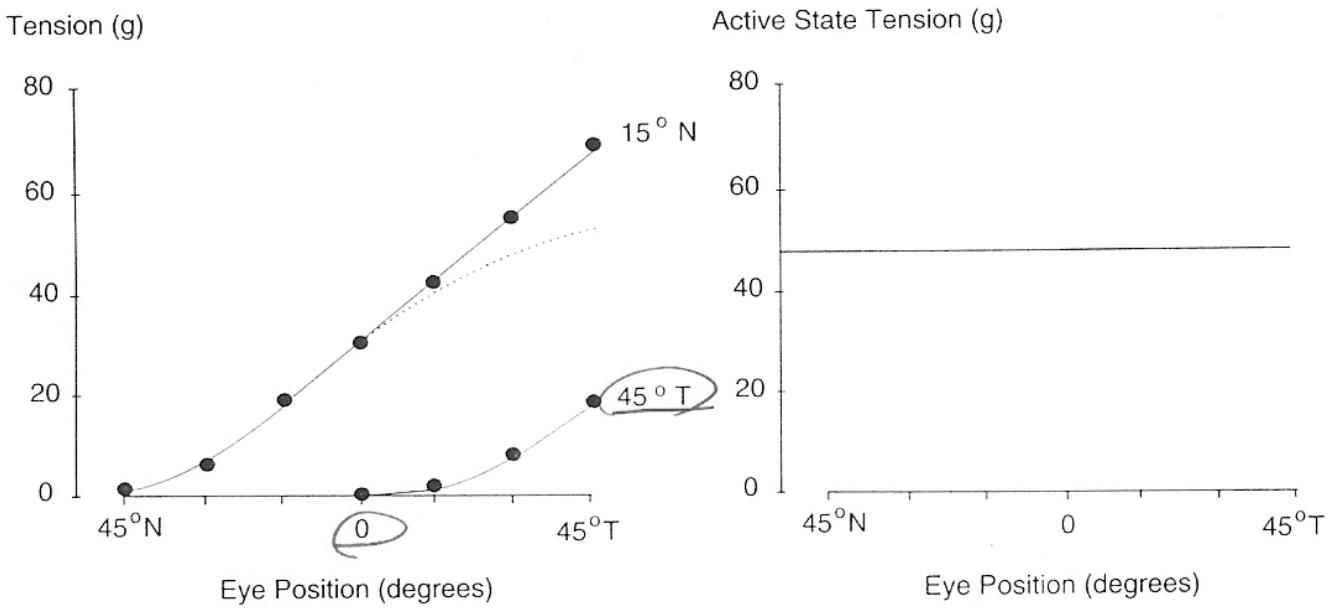
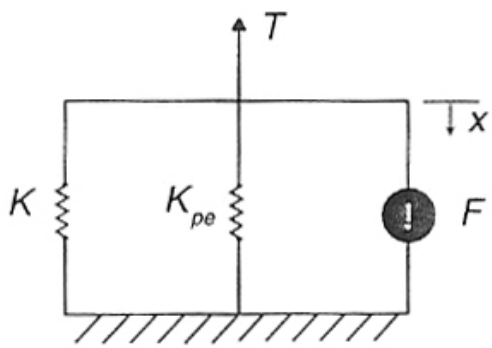


Fig. 7.10 Diagram illustrating the tension-displacement curve for unexcited muscle. The slope of the linear approximation to the data is muscle passive elasticity, K_{pe}.



$$T = F - K_{pe}\,x$$


Tension (g)
80
60
40
20
0
15° N
45° T
45°N
0
45°T
Eye Position (degrees)
Active State Tension (g)
80
60
40
20
0
45°N
0
45°T
Eye Position (degrees)


T
x
K
K_{pe}
F

$$T = F - K_{pe}\,x - Kx$$

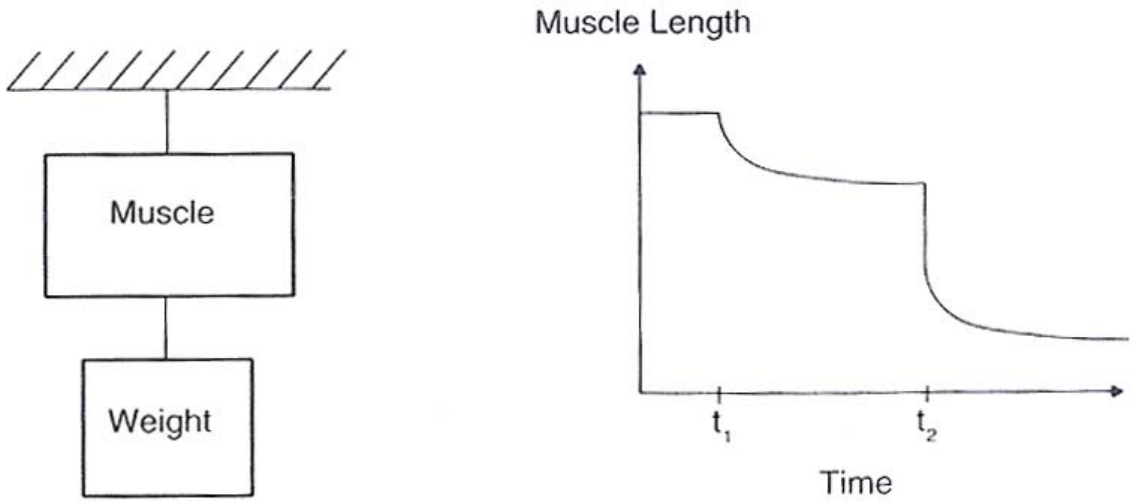
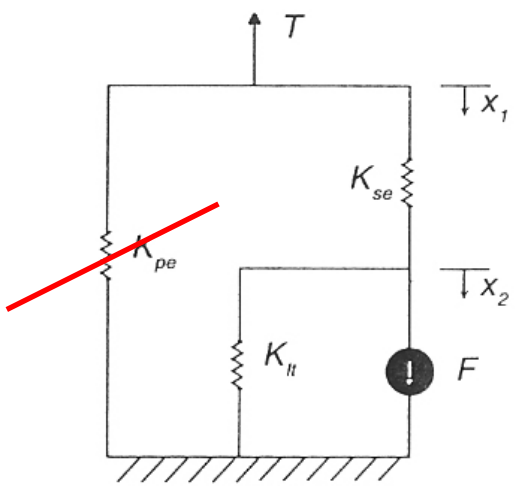


Fig. 7.15 Diagram illustrating the quick release experiment. (Left) The physical setup of the experiment. (Right) Typical data from the experiment. At time t_1 the muscle is fully stimulated and at time t_2 the weight is released.



$$T = K_{se}\,(x_2 - x_1)$$

$$F = K_{lt}\,x_2 + K_{se}\,(x_2 - x_1)$$

Viscous Properties of Muscle

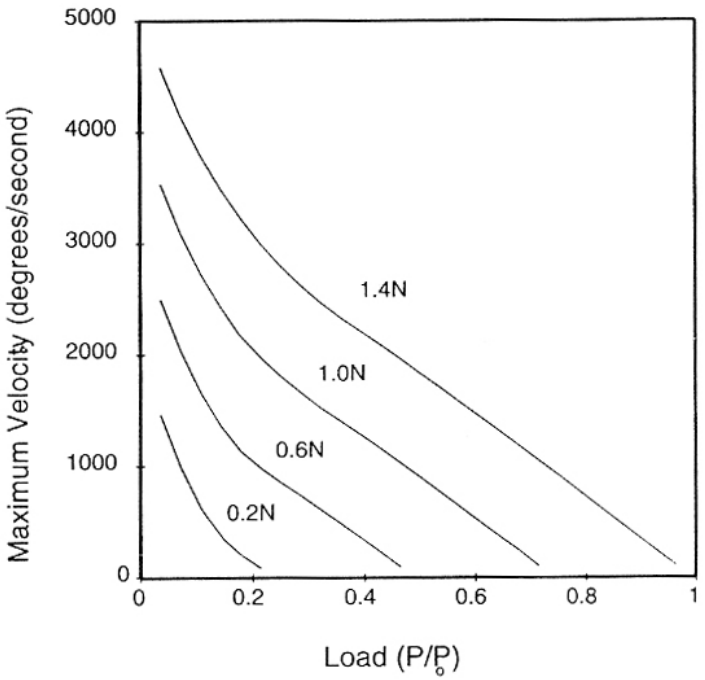
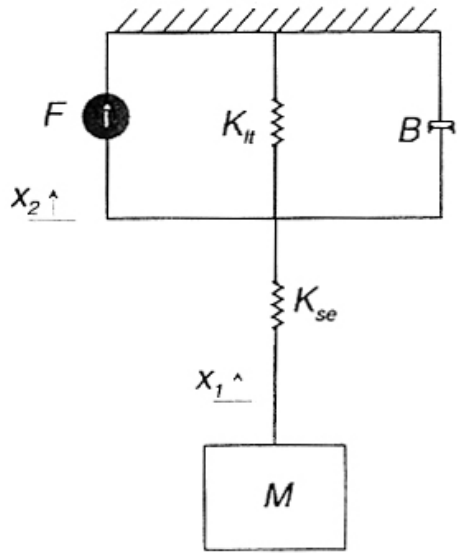


Fig. 7.21 Illustrative family of force–velocity curves for active-state tensions ranging from 1.4 to 0.2 N.



P = Mg

P_0 = isometric tension (the largest weight that the muscle can move)

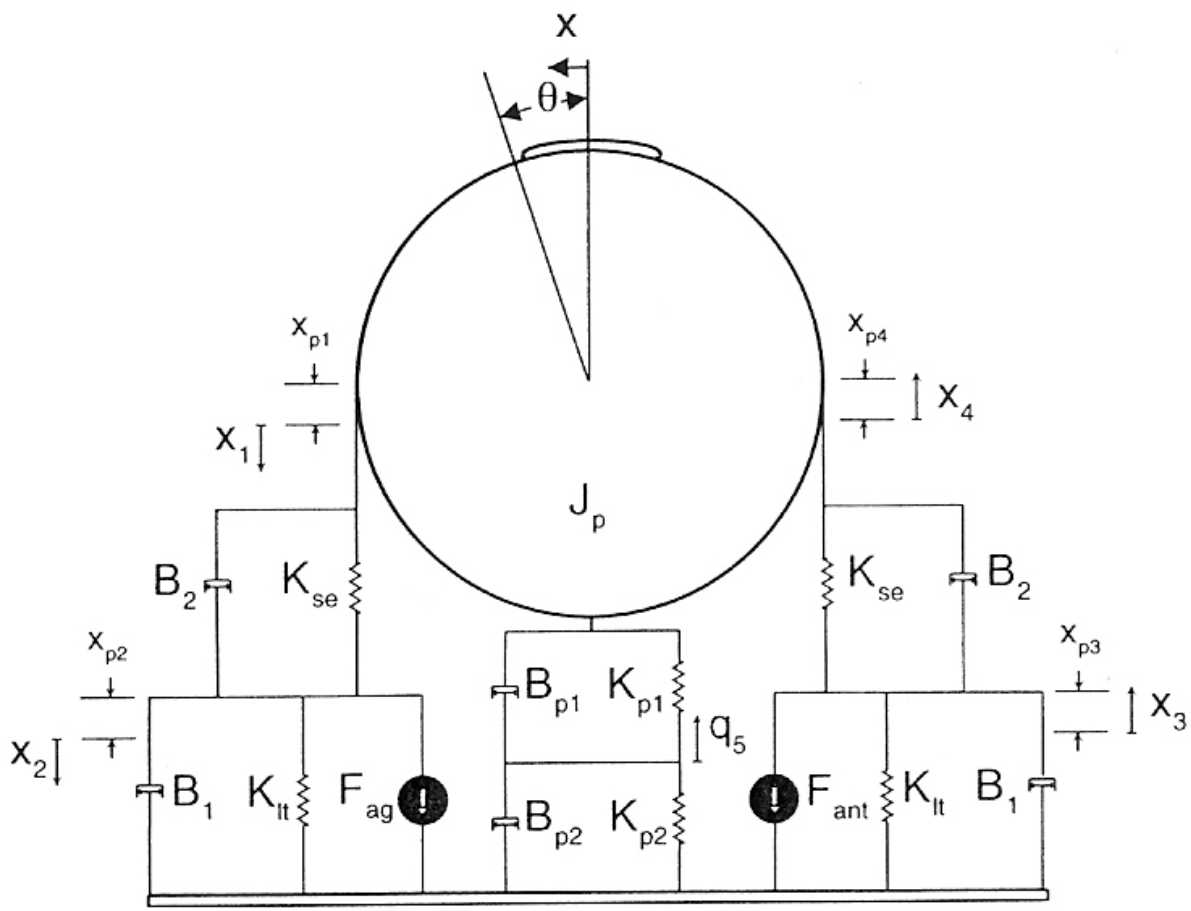
$$F = B\dot{x}_2 + K_{lt}x_2 + Mg$$

Solving previous equation for x_2 and $\dot{x}_2$ gives

$$x_2(t) = \frac{F - Mg}{K_{lt}}\left(1 - e^{\frac{-K_{lt}t}{B}}\right)$$

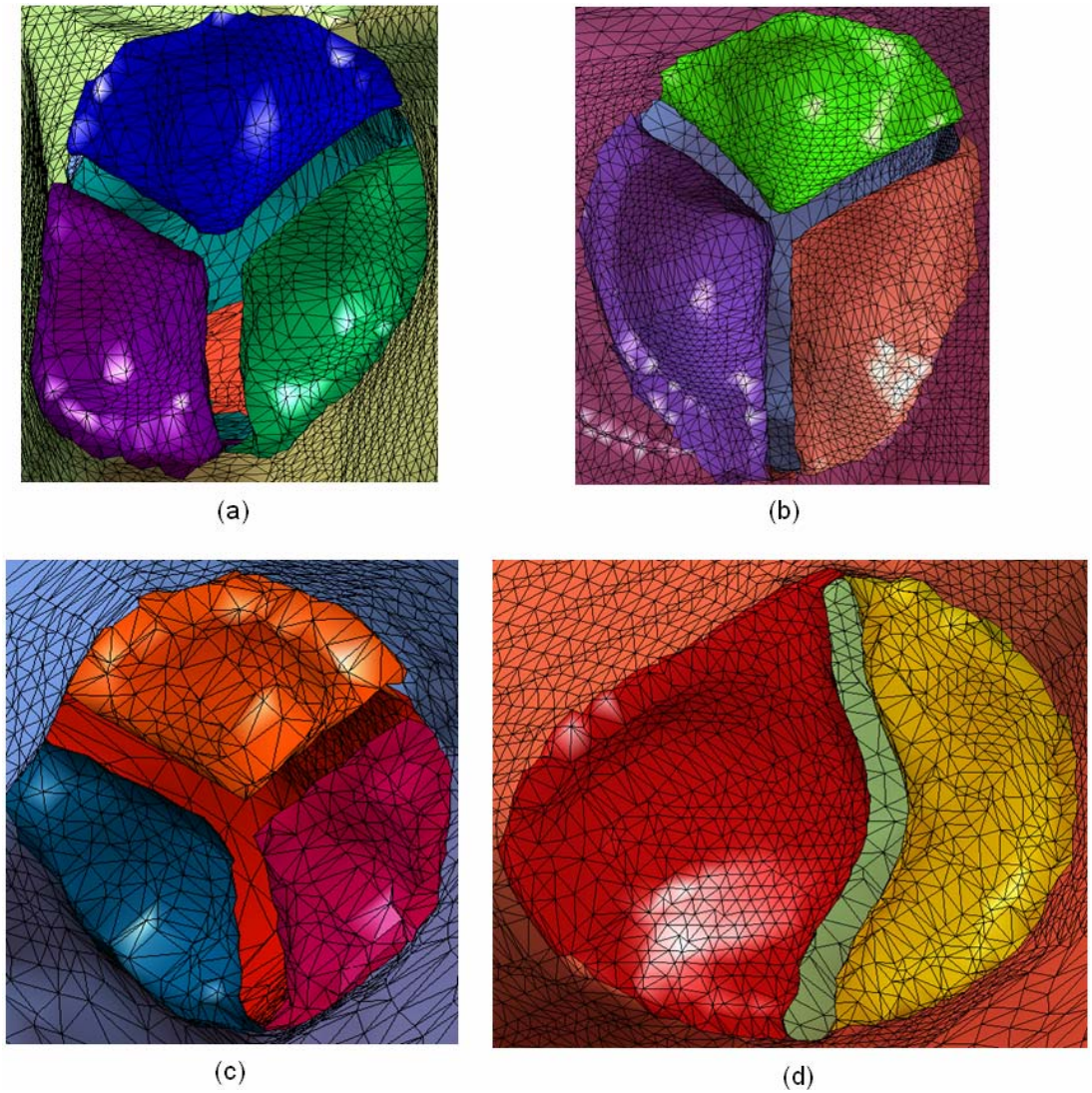
$$\dot{x}_2(t) = \frac{F - Mg}{B}e^{\frac{-K_{lt}t}{B}}$$

Truer Linear Homeomorphic Saccadic Eye Movement Model



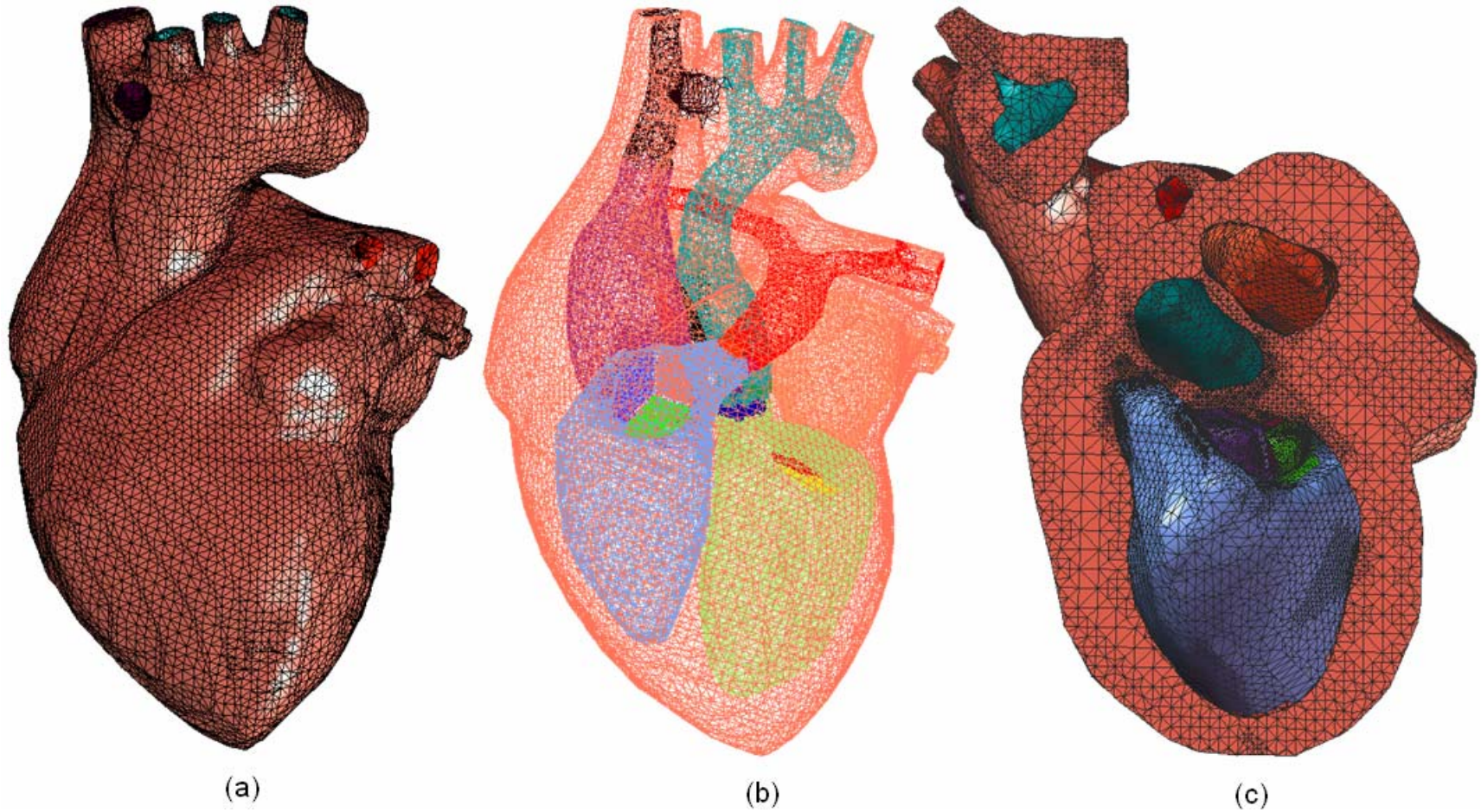
Finite Element Analysis

- Using numerical approximation to solve problems involving complicated geometries, loadings and material properties.
- The numerical method yields approximate values of the unknowns at discrete numbers of points in the continuum.
- Modeling a body by dividing it into an equivalent system of smaller bodies or units (finite elements) interconnected at points common to two or more elements (nodal points or nodes) and/or boundary lines and/or surfaces.
- Instead of solving the problem for the entire body in one operation, one formulates the equations for each finite element and combines them to obtain the solution of the whole body.



(a) - the aortic valve; (b) - the tricuspid valve; (c) - the pulmonary valve; (d) - the mitral valve.

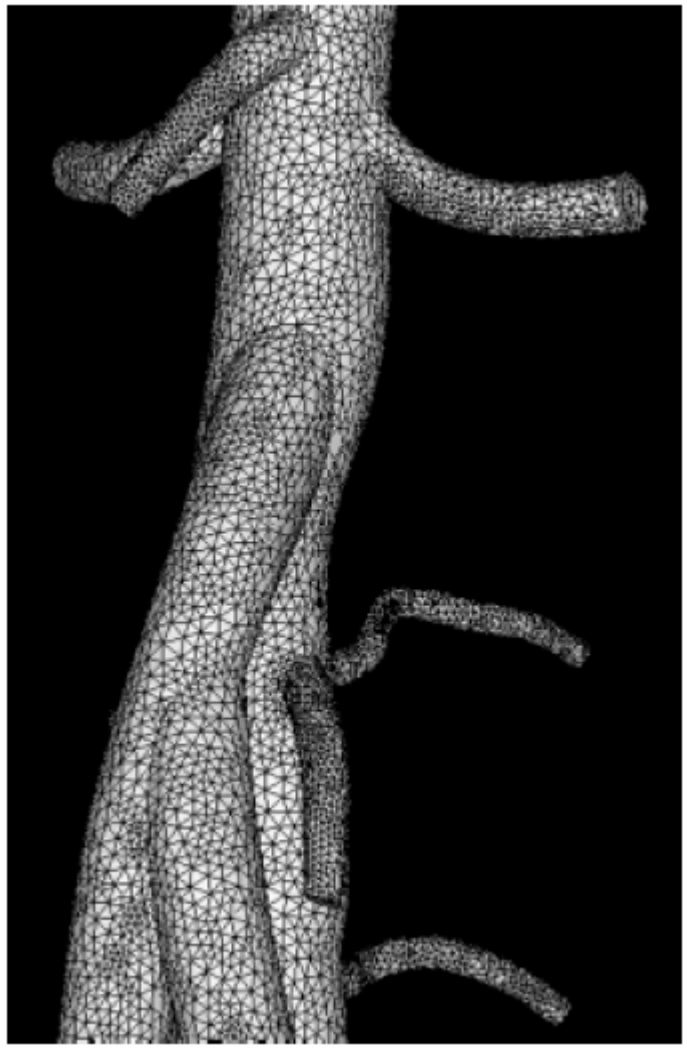
From: http://www.ices.utexas.edu/~jessica/paper/heart/



(a) the heart model viewed from outside; (b) the result of boundary detection in wireframe, each of the twenty-two components of the heart model is represented by a different color; (c) a cross section of the adaptive tetrahedral mesh

From: http://www.ices.utexas.edu/~jessica/paper/heart/

Fluid Dynamics and Finite Element



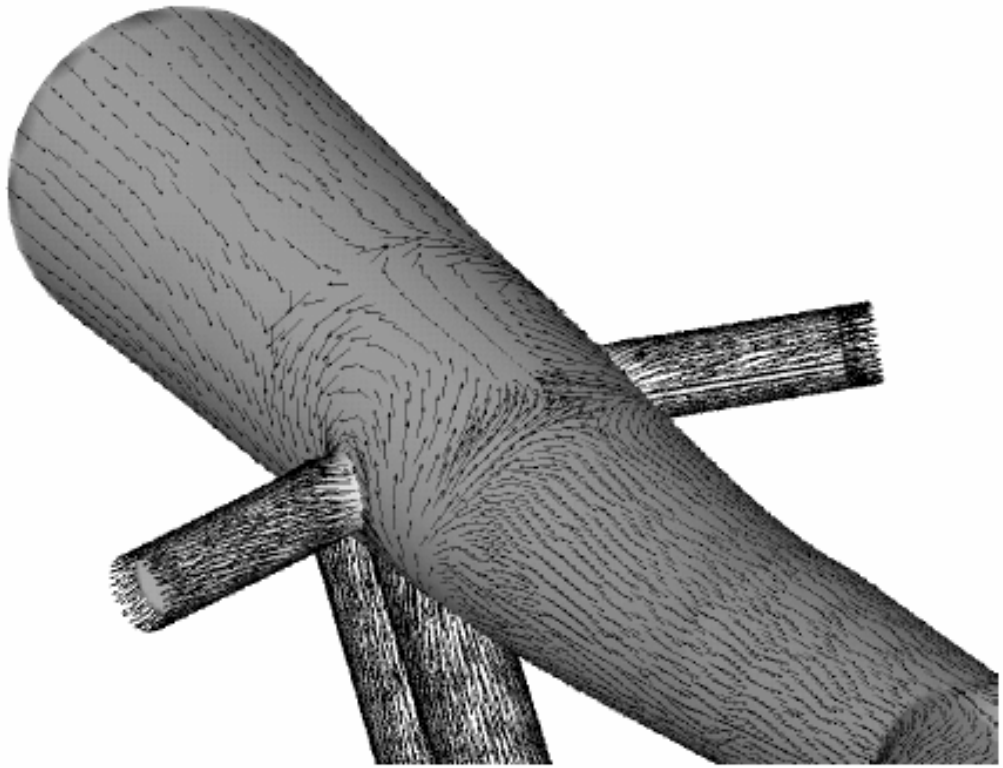


Figure 6: Mean surface traction vectors along the posterior wall of the abdominal aorta. Note the circumferential orientation of the mean surface traction vectors along the posterior wall of the aorta in the neighborhood of the renal arteries. From Taylor *et al*. [73].

Figure 14: Close-up view of proximal aorto-femoral bypass with end-to-side anastomosis. Velocity vectors and contours of velocity magnitude are shown on a slice plane through the anastomosis illustrating extraction of quantitative flow data for a vascular surgical plan.

Final Words for the Physiological Modeling

- 意義?
- 實驗驗證
- 簡單 vs 複雜

The End

Thank you for your attention